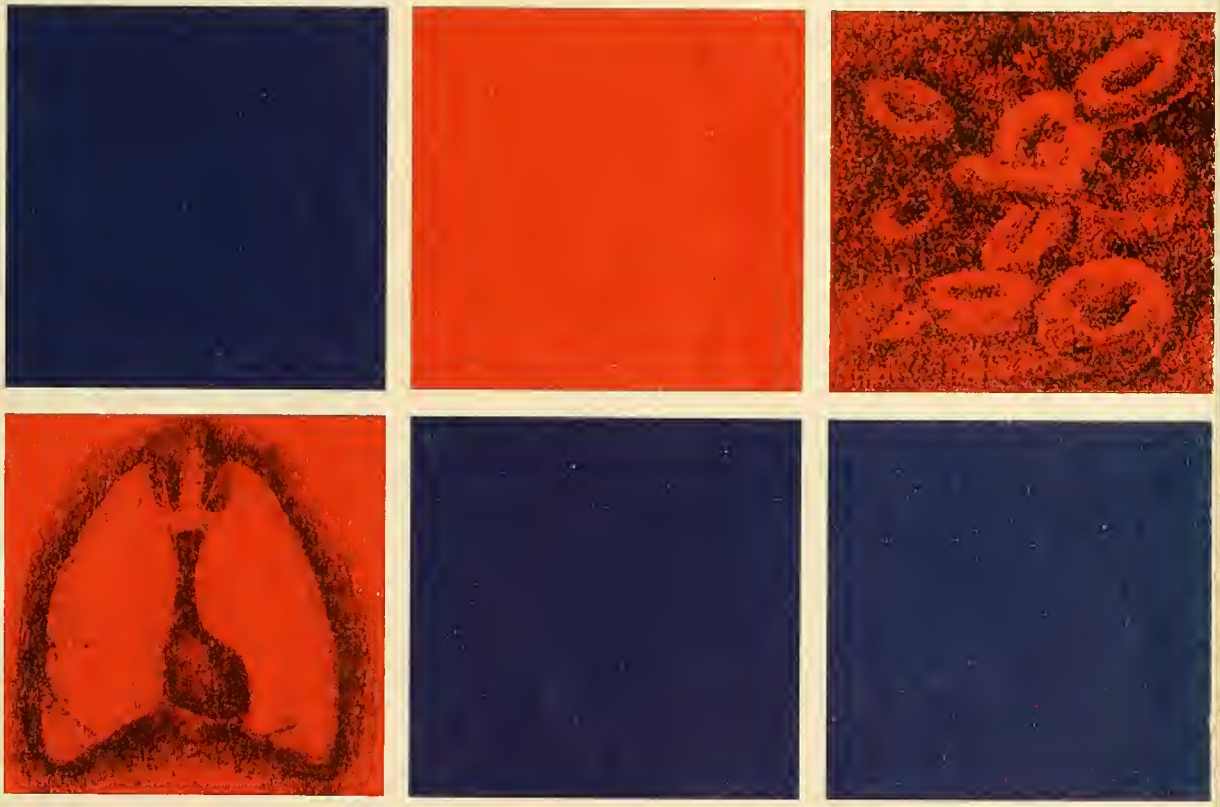
FIFTH REPORT OF THE DIRECTOR OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

FIFTH REPORT OF THE DIRECTOR OF THE NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

HEART, LUNG, AND BLOOD RESEARCH
FIVE YEARS OF PROGRESS: THE CHALLENGE AHEAD

February 28, 1978

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND 20014

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

February 28, 1978

The President
The White House
Washington, D. C.

Dear Mr. President:

I am submitting to you for transmittal to the Congress the Fifth Annual Report of the Director, National Heart, Lung, and Blood Institute. This Report not only marks the fifth anniversary of the National Heart, Blood Vessel, Lung, and Blood Program, but also the thirtieth anniversary of the establishment of the National Heart Institute, the forerunner of the National Heart, Lung, and Blood Institute. The Report outlines our progress over the past year, and our plan for the next five years. In addition, it discusses in detail the research progress made over the five years since the enactment of the National Heart, Blood Vessel, Lung, and Blood Program.

The progress now being made is most impressive, with a decline in cardiovascular death rates of over 30% since 1950 against a 19% decline for non-cardiovascular diseases. Despite an aging population, deaths due to cardiovascular disease are at the lowest point since 1964. Moreover, life expectancy is increasing with an average gain of one to two years for children born since 1972. The magnitude of the problem, however, remains great. Cardiovascular disease continues to be the nation's leading cause of death and continues to lead in economic cost -- $50.4 billion in 1975.

The Institute is encouraged that its efforts in fundamental and clinical research and the changes now being manifested nationally in diet and nutrition, hypertension awareness and control, smoking, emergency medical services, and other areas as well, will continue to decrease the disease toll. The progress achieved thus far reflects the determination of those who have worked to more fully understand the causes, treatment and prevention of heart, lung, and blood diseases. We feel confident that the next five years of this critical National Program will bring about equally significant progress.

Sincerely,

Robert I. Levy, M.D.
Director

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PREFACE

The National Heart, Lung, and Blood Institute (NHLBI) approaches the 30th anniversary of its existence as the nation's focus for research on cardiovascular diseases, and marks the 5th year since its authority was enlarged by Congress to advance the national attack on heart, blood vessel, lung, and blood diseases. It is therefore an appropriate time to reflect on the past and look forward toward the future: at the programs and accomplishments of the last five years; at the challenges faced by the NHLBI as it leads the national attack; and at the Institute's research strategy and programs designed to meet these challenges.

Accordingly, this, the *Fifth Report of the Director of the National Heart, Lung, and Blood Institute,* reviews the Institute's activities, progress, and accomplishments since passage of the National Heart, Blood Vessel, Lung, and Blood Disease Act of 1972 (PL 92-423); looks at Institute goals and programs for the period 1978–1982; summarizes legislative initiatives and resulting Institute mandates; describes program planning, evaluation, and coordination activities; and projects manpower and resource needs.

The primary focus of this report is on the scientific content of the Institute's biomedical research programs. These programs form the basis of the Institute's strategy to conduct, develop, and support activities which have as their ultimate objective *prevention* of cardiovascular, pulmonary, and blood diseases and effective control of their complications.

The report begins by examining the magnitude of the challenges faced by the NHLBI; describes the nature of the Institute's response to those challenges in terms of program strategy and program elements; and provides evidence of program impact in terms of reductions in morbidity and mortality and improvement in the quality of life. After reviewing the state of the science in 1972 and program goals for the period 1972–1977, each section describes accomplishments during that period, updates the state of the science to that in 1977, states program goals for the years 1978–1982, and outlines the research activities designed to meet those goals.

It is hoped that this report provides the reader with an appreciation of the enormity of the disease problems within the Institute's purview and of the magnitude, complexity, and scope of the research, evaluation, demonstration, education, and training programs which must be planned, implemented, and coordinated in order to have even a minimal effect on these disease problems. A task of these proportions requires a research program strategy comprising a spectrum of logical, integrated activities; resources commensurate with the size of the task; and sufficient time to permit the discovery, development, evaluation, demonstration, and translation of new knowledge.

Clearly, the cost in terms of manpower, money, and time is great. But the benefits are even greater —no less than improved health, increased longevity, and better quality of life for all Americans.

In Lipid Research Clinics across the nation, scientists such as this one are analyzing and recording serum glyceride levels. Triglycerides are one of the blood components known to influence the development of arteriosclerosis.

1. THE CHALLENGE AND THE RESPONSE

For more than 50 years, heart and blood vessel diseases have been the major causes of death in the United States, accounting for more than half of all deaths. Diseases of the lung also constitute a major national health problem, and blood diseases often lead to complications involving cardiovascular and pulmonary systems. The annual economic cost of these diseases is staggering; the emotional and social losses are immeasurable.

In 1948, the National Heart, Lung, and Blood Institute (NHLBI) was established (as the National Heart Institute) to reduce the toll of these major killer diseases through research. Since that time, the Institute's programs have expanded enormously in mandate and in scope. They have led to a number of discoveries which have improved the treatment, diagnosis, and most important, the prevention of these diseases. The results of the program now impact upon the lives of all Americans.

In this chapter, the nature of that program and examples of its achievements and impact are reviewed in the context of the magnitude and scope of the Institute's challenge and of the program strategy designed to respond to that challenge.

MAGNITUDE OF THE CHALLENGE

The NHLBI has the major responsibility for heart, blood vessel, lung, and blood diseases and blood resources research in this country. The enormity and significance of this responsibility and the challenge it represents can only be appreciated when considered in light of the morbidity, mortality, and economic costs associated with cardiovascular, pulmonary, and blood diseases, and of the need for an adequate supply of safe, high quality blood, whenever and wherever it is needed.

- Each day, an estimated 3,400 Americans—more than two each minute—suffer a heart attack.
- Approximately 1,600 people suffer strokes each day.
- An estimated 23 million to 27 million Americans have hypertension, a major risk factor for heart attack and stroke.
- Some 25,000 children are born with defective hearts each year.
- Over 100,000 children and 1.7 million adults have rheumatic heart disease.
- More than 14 million people are victims of chronic lung diseases.
- For every 1,000 live births, from 5 to 10 babies die of respiratory distress syndrome of the newborn.
- About 50,000 Americans suffer from sickle cell disease.
- Each year, well over 12 million units of blood are collected for transfusion and for preparation of plasma fractions.
- Post-transfusion hepatitis affects thousands of blood recipients resulting in incapacitating illness lasting weeks or months.

In fact, of the 10 leading causes of death in the U.S., four fall within the purview of the NHLBI—heart disease (including coronary heart disease, hypertensive heart disease, congenital heart disease, and rheumatic heart disease), stroke, major lung diseases, and arteriosclerosis. In 1975, these diseases accounted for 980,230 deaths, more than half of all deaths that year (Table 1). Preliminary data from 1976 show that the same relationships hold.

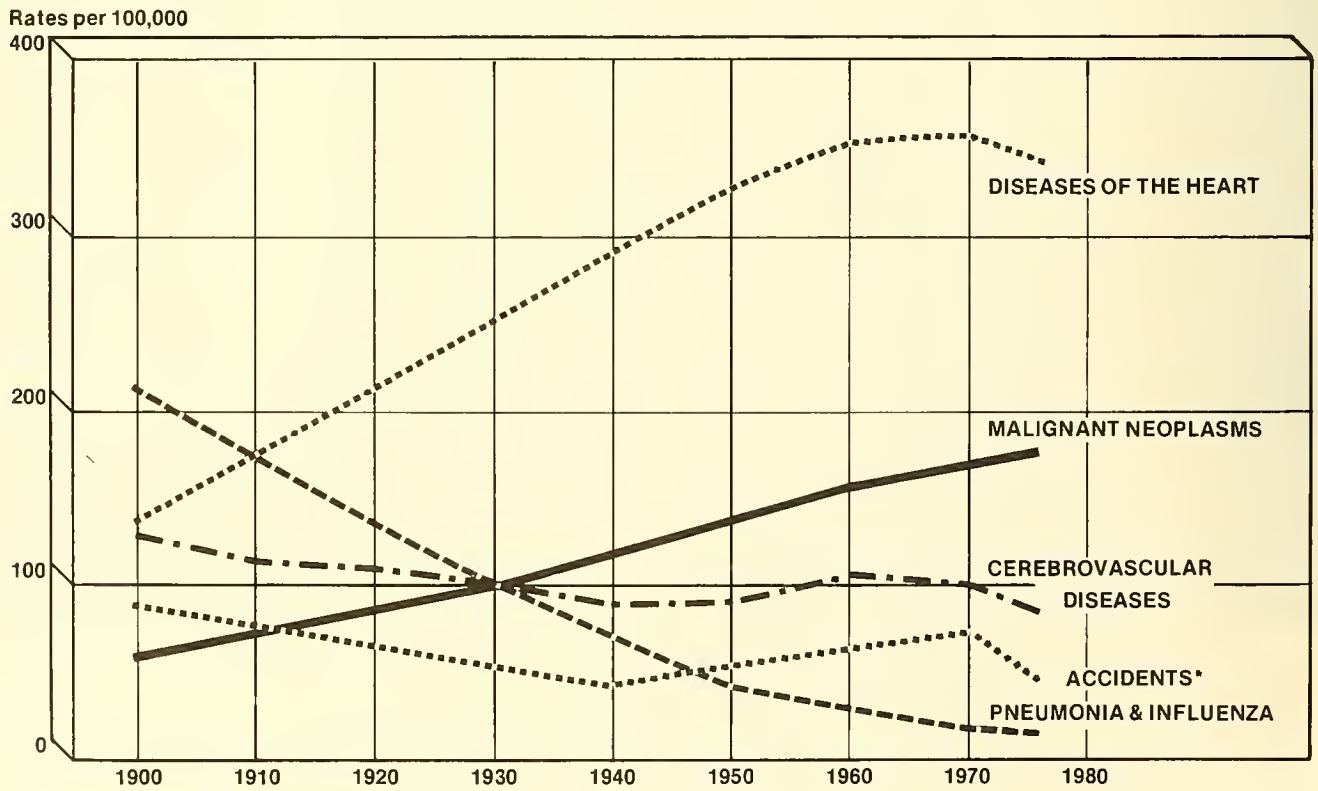
One of these diseases, heart disease, has topped the list of the nation's killers for several decades. Since early in this century, diseases of the heart have been the leading causes of death (Figure 1). And they remain so today in spite of a steady decline in heart disease death rates since the 1950's. In 1975, for example, heart disease was responsible for 716,205 deaths (Table 1).

Table 1

LEADING CAUSES OF DEATH IN THE UNITED STATES, 1975

	Deaths	Percent of Total Deaths
1. Heart Disease	716,205	37.8
2. Cancer	365,693	19.3
3. Stroke	194,038	10.3
4. Accidents	103,030	5.4
5. Influenza-Pneumonia	55,664	2.9
6. Lung Diseases (Chronic Obstructive Pulmonary Diseases)	41,100	2.2
7. Diabetes	35,320	1.9
8. Cirrhosis of the Liver	31,623	1.7
9. Arteriosclerosis	28,887	1.5
10. Suicides	27,063	1.4
Total	1,598,623	84.5
Other Deaths	294,256	15.5
Total Deaths	1,892,879	100.0

Figure 1: FIVE LEADING CAUSES OF DEATH IN THE U.S., 1900-1976



*Excludes motor vehicle accidents in 1940.

Table 2

TOTAL ECONOMIC COST OF SELECTED DISEASES, 1972 AND 1975
(Dollars in Billions)

Diagnosis	Total		Direct Costs		Indirect Costs			
					Morbidity		Mortality	
	1972	1975	1972	1975	1972	1975	1972	1975
Diseases of the Circulatory System	40.1	50.4	10.9	16.0	6.4	8.7	22.7	25.7
Diseases of the Respiratory System	16.5	19.7	5.9	7.6	7.1	8.5	3.4	3.6
Diseases of the Blood and Blood-Forming Organs	0.9	1.3	0.5	0.7	0.2	0.3	0.2	0.3
Subtotal	57.5	71.4	17.3	24.3	13.7	17.5	26.3	29.6
All Other	131.3	174.0	57.9	75.2	28.6.	40.3	44.9	58.5
Total	188.8	245.4	75.2	99.5	42.3	57.8	71.2	88.1

Sources: National Center for Health Statistics; Public Services Laboratory, Georgetown University.

Another of these diseases—respiratory disease—was the disorder treated most frequently in office-based medical practice during 1975, according to a recently released study by the National Center for Health Statistics. This study of ambulatory care rendered in physicians' offices in 1975 shows that:

- Diseases of the respiratory system—including chronic diseases such as emphysema as well as colds and hay fever—accounted for 14 percent of all physician's visits
- Diseases of the circulatory system, including heart disease, were next most frequent with 10 percent of all visits.

The economic toll of these diseases is staggering. In 1975, the direct cost (including hospitalization costs, physician fees, and drugs) for diseases of the circulatory and respiratory systems and diseases of the blood and blood-forming elements totaled $24.3 billion (Table 2). Indirect costs of morbidity, including the economic value of days lost from work, add another $17.5 billion to that yearly toll. Although the indirect costs of mortality are difficult to quantify, it is estimated that an additional $29.6 billion was lost in 1975 in productivity alone. Thus, the estimated total economic toll due to diseases of the circulatory system and respiratory systems and of the blood and blood-forming organs was $71.4 billion in 1975. Recognition of the magnitude of the costs for these diseases helps place the health problems of our country in perspective with other pressing social problems.

RESPONSE TO THE CHALLENGE

Program Growth and Evolution

As the magnitude of disease problems has grown and as research results have made clear the potential for improving the nation's health, the Institute's mandates and resources have expanded well beyond those of the original National Heart Institute when it was established in 1948 to assume primary responsibility for Federal programs in the cardiovascular disease field. In 1969, in response to the continuing seriousness of lung diseases, the Institute's mandate was enlarged to encompass research and training on respiratory diseases, and its name was changed to the National Heart and Lung Institute.

A major juncture in the Institute's development was the passage, in 1972, of the National Heart, Blood Vessel, Lung, and Blood Act (PL 92–423), which provided for expanded, intensified, and coordinated efforts against heart, blood vessel, lung, and blood diseases. Through this Act, Congress mandated the development of a National Program of research, prevention, education, and control to focus

on these diseases and designated the Institute to lead and coordinate the implementation of that plan.

In 1976, legislation extended the authority of the 1972 Act for two additional years, provided for increased emphasis on programs in blood research and in the management of the nation's blood resource, and redesignated the Institute the National Heart, Lung, and Blood Institute. Under the legislation, the primary missions of the NHLBI are to:

- Conduct and support research to increase fundamental and clinical knowledge about the cardiovascular, pulmonary, and blood systems and blood resources.
- Develop new and improved techniques for preventing, diagnosing, and treating diseases affecting these systems.
- Carry out clinical testing and evaluation of new knowledge and techniques which show promise of facilitating disease prevention, diagnosis, and therapy.
- Encourage the application of proven techniques by the medical and research communities.
- Support the training of scientists, clinicians, and teachers in the cardiovascular, pulmonary, and blood fields.
- Conduct a comprehensive program of education and demonstrations to inform the general public and health professionals about research and clinical advances related to Institute programs.

As the Institute's mandates and programs have been expanded and shaped over the nearly 30 years of its existence, the structure of the NHLBI has been modified to maximize its responsiveness and effectiveness. Currently, as the result of the 1972 Act and the 1976 reauthorization, research related to cardiovascular diseases, lung diseases, and blood diseases and blood resources is supported by three major extramural programmatic divisions. Responsibility for the 20 program elements in the National Heart, Blood Vessel, Lung, and Blood Program is divided among these divisions as outlined in Table 3.

The size and distribution of the budget have also changed significantly during the Institute's development. The initial budget for the newly formed National Heart Institute was $15 million in 1948. The National Heart and Lung Institute's budget was $230 million in 1972. In 1977, the NHLBI's budget totaled $396 million.

Because the Institute's programs are designed to be responsive both to national need and to research advances and opportunities, it is not surprising that the distribution of its financial resources has changed over the years. For example, large-scale clinical trials, which became a part of the Institute's program relatively recently, have expanded as basic and clinical research results have warranted to the point that they now account for approximately 12 percent of the Institute's annual obligations.

Table 3

NATIONAL PROGRAM ELEMENTS BY DIVISION

Heart and Vascular Diseases	Lung Diseases	Blood Diseases and Resources
Arteriosclerosis	Structure and Function of the Lung	Bleeding and Clotting Disorders
Hypertension	Emphysema and Chronic Bronchitis	Red Blood Cell Disorders
Cerebrovascular Disease	Pediatric Pulmonary Diseases	Sickle Cell Disease
Coronary Heart Disease	Fibrotic and Immunologic Lung Diseases	Blood Resources
Peripheral Vascular Disease	Respiratory Failure	
Arrhythmias	Pulmonary Vascular Diseases	
Heart Failure and Shock		
Congenital and Rheumatic Heart Diseases		
Cardiomyopathies and Infections of the Heart		
Circulatory Assistance		

Program Strategy

A primary mission of the NHLBI is to conduct, develop, and support programs which have as their ultimate objectives prevention of cardiovascular, pulmonary, and blood diseases, and effective control of their complications.

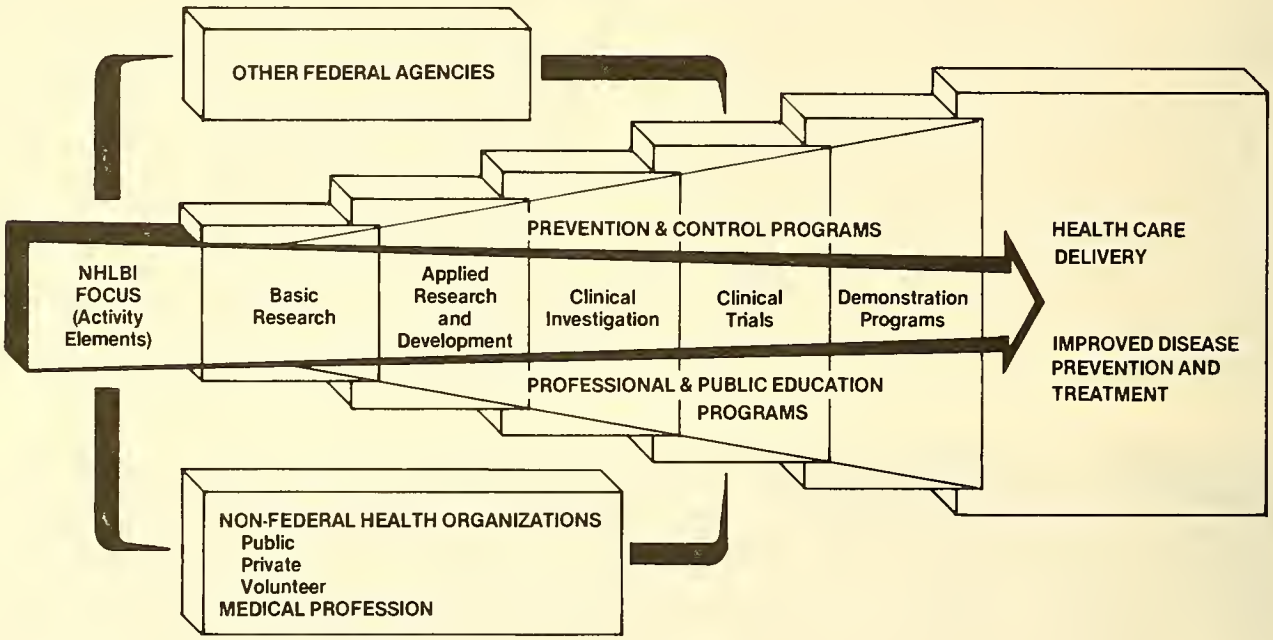
The NHLBI believes that prevention offers the greatest promise of reducing death and disability from disease and thus relieving the concomitant individual, social, and economic burdens. Accordingly, between 15 percent and 20 percent of the current NHLBI budget supports research, education, and demonstration projects directly related to disease prevention.

Yet it is necessary to be realistic. As demonstrated earlier in this chapter, millions of people are currently afflicted, or at risk of being afflicted, with the disorders included within the Institute's purview. Thus, although prevention is the primary goal, we must continue to discover and develop new and improved means for controlling the painful and disabling complications of disease.

Furthermore, disease prevention cannot be successfully achieved in the absence of a thorough understanding of the basic etiology and pathophysiology of the target disease and of the roles and interactions of identified risk factors. Only with such an understanding can we proceed to determine the

Comprehensive health care is based on prevention of disease as well as treatment, and should include routine blood pressure measurement for all ages — even small children.

Figure 2: THE BIOMEDICAL RESEARCH SPECTRUM



efficacy and safety of various approaches to removing or reducing risk factors through life-style changes or therapeutic regimens.

Thus, the NHLBI pursues its goal of disease prevention and control through a coordinated program strategy comprising a logical progression of activities from basic research on fundamental life processes and mechanisms to practical demonstrations of the clinical applicability of new findings. That strategy is idealized in the biomedical research program strategy described graphically in Figure 2.

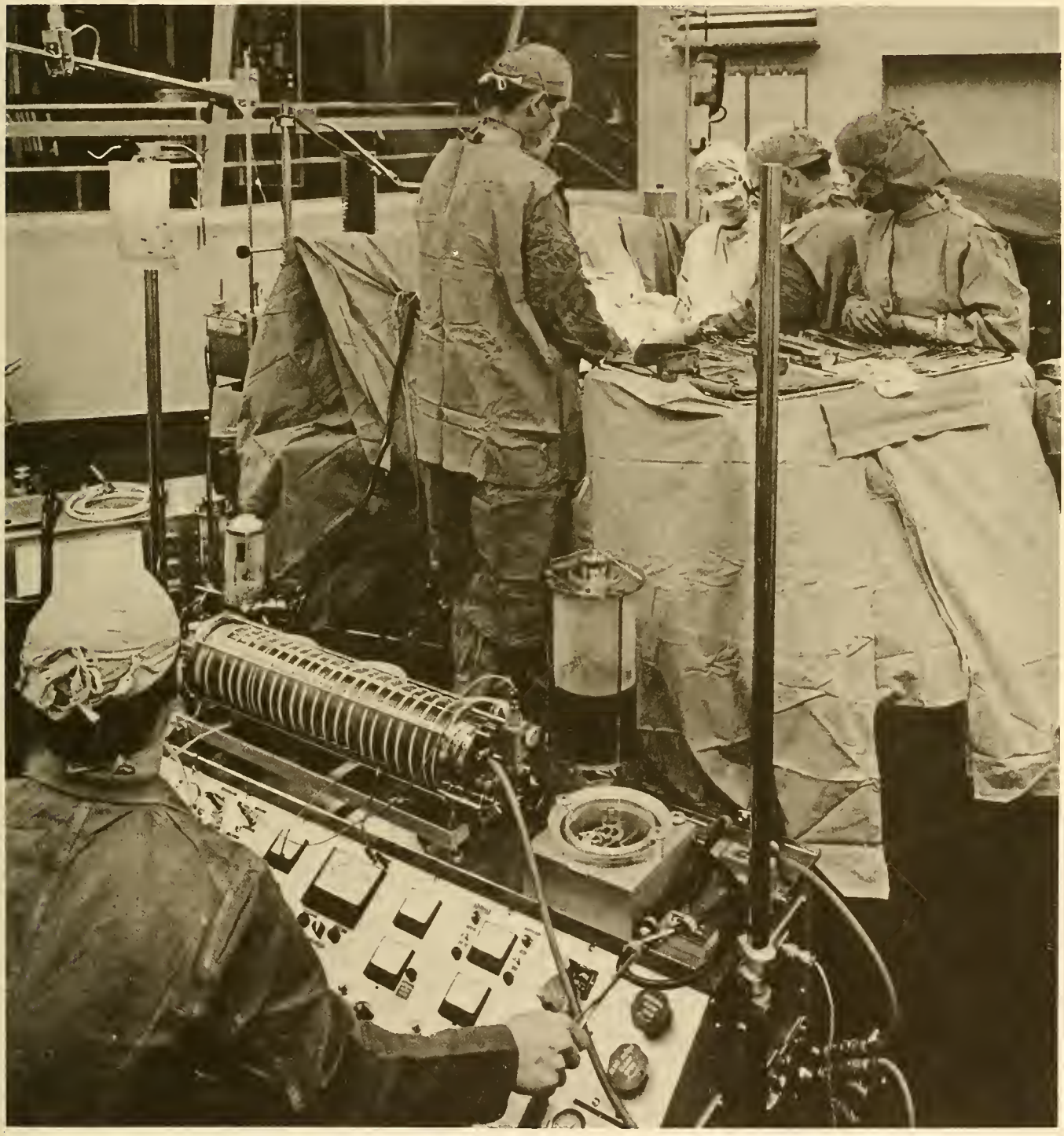
The foundation of the research program is basic research. From such research is derived the necessary knowledge of disease etiology and pathogenesis that eventually leads to applied research and development on specific disease problems. Clinical investigation translates fundamental knowledge to treatment and prevention regimens which may require major testing in clinical trials. Demonstration programs test the feasibility of mounting prevention, treatment, and education programs in specific settings.

And, in general, important clinical advances are preceded by research on fundamental mechanisms —studies of animals, plants, tissues, cells, or subcellular components—so that once a firm basis of knowledge has been established, its application on the clinical level becomes possible.

Nevertheless, the process by which medical advances occur is not a simple linear progression. Rather, the process is complex, iterative, and dynamic, and its components are interdependent and overlapping. There are many different entry points to the process, feedback from one component to previous ones abounds, and the lines separating components are often unclear.

Figure 2, then, depicts the overall direction of the activities through which the Institute pursues the goals of the National Program, but does not adequately depict the dynamic nature of the process nor the interdependence of its component steps. Yet one must understand this process to appreciate how the many activities conducted and sponsored by the NHLBI contribute to the ultimate achievement of those goals.

It is also important to understand the magnitude of the national effort required to reduce death and disability due to diseases of the heart, lung, and blood. It is a mammoth project involving years of painstaking research by dedicated individuals in



The development of highly efficient heart-lung machines, which are capable of temporarily substituting for the function of the patient's heart and lungs, has enabled surgeons to undertake delicate heart repairs in a bloodless field.

laboratories around the country, extensive clinical trials and community field studies, demonstration and control programs, and professional and public education efforts.

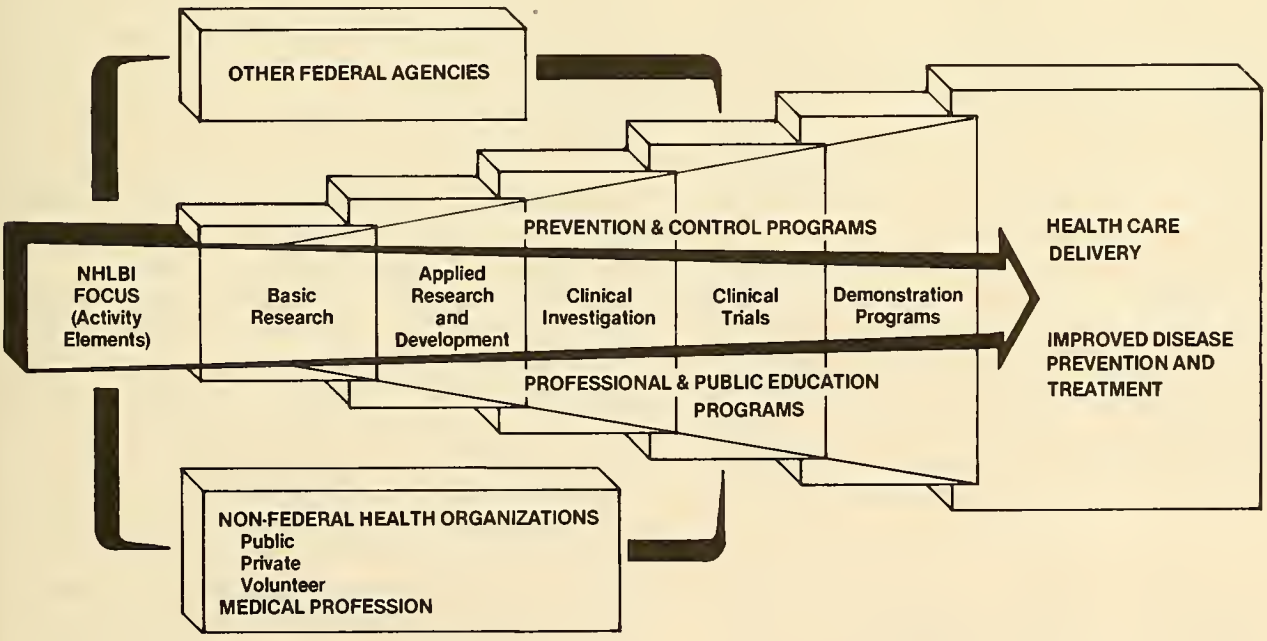
And it is an effort requiring contributions by diverse organizations and groups throughout the country. Figure 2 illustrates the important relationships between the NHLBI and other Federal agencies and non-Federal health organizations and professional associations. These relationships, and the significant contributions made to NHLBI programs by these agencies, organizations, and associations, greatly facilitate progress toward achieving the Institute's goals.

2. ACCOMPLISHMENTS AND HIGHLIGHTS: 1977

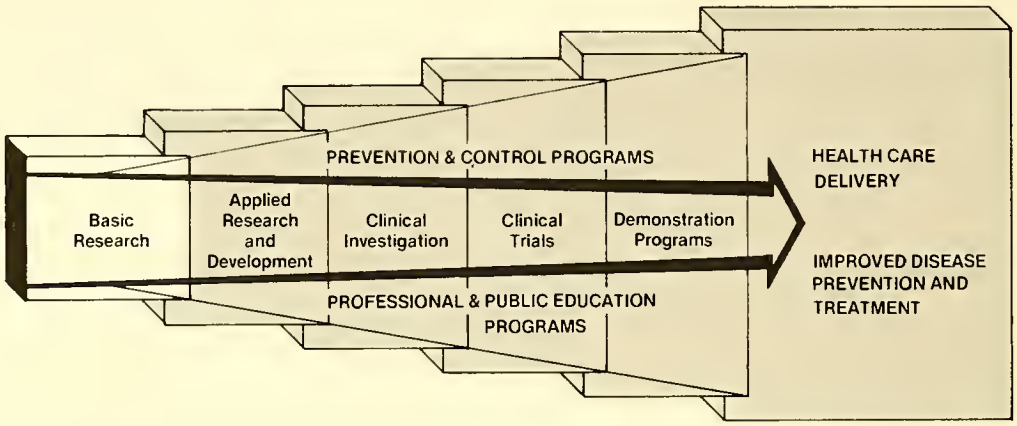
Because of the nature of the research process represented by Figure 2, advances in biomedical research do not suddenly emerge, but rather evolve and develop over a period of time. Thus, it is most difficult to identify specific research accomplishments during a certain time period.

With this constraint in mind, NHLBI program staff members have selected research program highlights of 1977 which they feel represent significant progress in specific areas of Institute concern.

These selected highlights illustrate the Institute's overall research program strategy, indicate the scope and diversity of the programs under the Institute's aegis, and demonstrate the value of a coordinated approach combining the several elements of the research spectrum of Figure 2.



BASIC RESEARCH



Basic research is systematic, intensive study directed toward greater knowledge or understanding of a specific subject. It is a long-range quest to augment the underlying conceptual structure in a research area.

Basic *biomedical* research deals with the structure and function of molecules, organelles, cells, tissues, organisms, and populations of man—or of suitable non-human models—in health and disease.

New biomedical knowledge through investigative research is the primary prerequisite for the development of methods for the prevention and treatment of disease. Creative research by both individual investigators and by teams of investigators is leading to new knowledge about heart, blood vessel, lung, and blood diseases.

As the foundation of the Institute Program, basic research on disease etiology and pathogenesis receives the major portion of the Institute's resources. This research has resulted in a number of significant concepts, theories, and discoveries which, in turn, have become the basis for further research, refinement, development, evaluation, and dissemination to the medical and public communities.

PLASMA LIPOPROTEINS

. . . Elucidation of Structure and Function

Lipoproteins are the vehicles for transporting lipids (fats) in the blood. How and why the specific protein moieties of the plasma lipoproteins (lipoprotein apoproteins) bind and solubilize the otherwise insoluble lipid has not been clear. Recently, the combined efforts of many scientists have culminated in determining the amino acid sequence and secondary and tertiary structure of the protein portion of several lipoprotein apoproteins. Seven different apoproteins have been described. Five of these have been completely sequenced, and the nature of their lipid binding has been defined. It has been found that these proteins orient themselves in solution as to specific hydrophobic (lipid solubilizing) and hydrophilic amino acid regions. Now that we have a better understanding of the lipid binding properties of these apoproteins, we will be able to synthesize proteins that may have even better lipid binding capabilities and possible therapeutic utility.

The enzyme lipoprotein lipase catalyzes the hydrolysis of triglycerides of very low density lipoproteins, releasing glycerol and fatty acids for cell storage and energy. This enzyme, however, requires a specific lipoprotein apoprotein apo C-II for maximal activity. Recently, the amino acid sequence of the apoprotein C-II fragment has been deduced and synthesized. The synthesis of the apo C-II fragment and the identification of the specific portion which is necessary for activation of the lipase represent an important breakthrough in our understanding of the mechanisms governing the hydrolysis of triglycerides in the blood.

ATHEROGENESIS

. . . Blood Platelet and Vessel Wall Interaction

Three important recent discoveries have greatly advanced our understanding of the genesis of atherosclerosis and may provide the basis for developing pharmacological agents to prevent or control it.

Many scientists believe that mature atherosclerotic plaques are monoclonal; that is, they have arisen from a single mutated cell. If this proves to be true, then all cells within a plaque are uniform in biochemical and cellular features and therefore should respond uniformly to pharmacological agents.

The injury theory of plaque development suggests that various kinds of injury to the endothelial tissue lining a blood vessel wall are followed by an interaction at the point of injury between blood platelets and smooth muscle cells. It has been demonstrated that a factor in platelets stimulates the smooth muscle cells to proliferate and aggregate, forming plaques. Decreasing the availability of platelets or employing anti-platelet aggregating drugs may inhibit the cellular proliferation reaction so that plaques do not develop, or develop to a lesser extent. Platelet modulation of smooth muscle cell proliferation after endothelial injury may, therefore, be an important early aspect of atherogenesis.

The discovery of prostacyclin, a potent inhibitor of platelet aggregation, has provided new insights into how atherogenesis may be triggered. Both prostacyclin and thromboxane are derived from the same source—prostaglandin endoperoxide—but they have antagonistic roles in the process of platelet aggregation. One hypothesis is that when platelets bump against the lining of a blood vessel wall, the platelets release prostaglandin endoperoxides. In turn, an intact vessel releases an enzyme that enables the endoperoxide to be converted to prostacyclin, thus inhibiting platelet aggregation. A damaged lining, however, does not release the enzyme. And, in its absence, the endoperoxides are converted to thromboxane, a substance which stimulates platelet aggregation. The action of thromboxanes was partially understood prior to the discovery of prostacyclin; however, why coagulation occurred in some instances but not in others was not known. These recent findings provide direction for further studies to elucidate the interactive role of blood platelets and the vessel wall in the genesis of atherosclerosis.

HIGH DENSITY LIPID LEVELS IN SERUM

. . . An Anti-Risk Factor of Coronary Heart Disease

There is increasing evidence that the level of high density lipoprotein (HDL) in the blood is inversely, strongly, and independently correlated with the risk of developing coronary heart disease. The higher the level of HDL in the serum, the lower the risk. This conclusion has been strengthened by new epidemiological, clinical, and animal studies. Recent biochemical evidence suggests that HDL may remove cholesterol from arterial walls or prevent it from depositing there. This finding is important since it may open the way to new types of therapy.

PROSTAGLANDINS AND HYPERTENSION

. . . Animal Studies Show Possible Causal Relationship

Prostaglandin E_2, the principal renal prostaglandin, is released from the kidney by norepinephrine. Normally, prostaglandins have a vasodilator effect; in rats, however, prostaglandins of the E series have a vasoconstrictor effect. A recent study suggests that these prostaglandins contribute to the development of spontaneous hypertension in one model of genetically hypertensive rats. These rats have a deficiency in an enzyme which normally inactivates prostaglandin. Without this control mechanism, the vasoconstrictor effect of norepinephrine is augmented and exaggerated and renal vascular resistance is increased—a possible initiating factor in the development of hypertension in these rats.

The enzyme deficiency responsible for the chain of events leading to increased renal vascular tension could be the inherited abnormality primarily responsible for the development of hypertension in these animals. In addition, this is the first time that the prostaglandin system has been directly related to the development of hypertension. It provides direction for future research into the causes of this chronic condition.

STRUCTURAL COMPONENTS OF THE LUNG

. . . New Understanding

Connective tissue components in the lung are of primary importance in the regulation of bronchial

development, in the maintenance of airway shape and continuity, and in the determination of the visco-elastic properties of lung tissue. The role of collagen and elastic fibers in the pathogenesis of numerous lung diseases is becoming clearer as the result of new information about these connective tissue components. At least four genetically distinct types of collagen are present in lung tissues, and there appears to be a specific pattern of distribution of different types in different parts of the lung. There is also evidence that different collagens appear at different times during lung development. Elastic fibers have two distinct components, one with a definite tubular structure (microfibrils), the other (elastin), filling the spaces between the microfibrils. These two components do not appear simultaneously during development; the microfibrils appear first, followed by the amorphous elastin. Evidence suggests that collagen exercises a controlling influence on the biosynthesis of elastin fibers. There are two other important components of lung connective tissue: proteoglycans and basement membrane. Because very little is known about them, a new program has been initiated to study the biochemistry of lung proteoglycans, and an international workshop is being planned on basement membrane. New information on the interaction between collagen and elastin fibers and on the biochemistry of proteoglycans and basement membrane should provide important insights into the development of normal lung structure as well as the pathogenesis of such diseases as emphysema and pulmonary fibrosis.

NEW UNDERSTANDING OF GENETIC PREDISPOSITION TO EMPHYSEMA

. . . Isolation and Properties of Antiproteases

Certain patients with emphysema exhibit a genetic deficiency that manifests itself in lower serum concentrations of the antiprotease alpha-1-antitrypsin (A_1AT) than those found in normal individuals. The exact biochemical error of the genetic mutation has now been identified: The difference between A_1AT in normal individuals and in individuals with a deficiency of A_1AT resides in the substitution of two amino acids in the protein portion of the molecule. New methods of purification involving a gel electrophoresis system now make it possible to isolate A_1AT variants from 50 ml of serum in 60 percent to 70 percent yield in about 36 hours. To date, 24 different variants of A_1AT have been identified. Since antiproteases like A_1AT constitute the main line of defense against protein breakdown of lung tissue, isolation and purification of these genetic variants advance our understanding of exactly what goes wrong in individuals with a genetic predisposition to emphysema.

CYSTIC FIBROSIS

. . . Factors Unique to Cystic Fibrosis Genotypes

Cystic fibrosis is the most widespread recessively inherited disease among white Americans. Yet to date, it is incurable, its carriers cannot be readily detected, and the basic biochemical defect is not known. Recently, however, it was suggested that the serum, saliva, urine, and sweat of individuals with cystic fibrosis contain a substance or substances which inhibit ciliary activity. In addition, the media of cultured fibroblasts taken from cystic fibrosis patients and from their parents both contain a similar factor or factors, although the parents as carriers only have one defective gene. This factor or factors has not yet been purified or isolated in sufficient quantity to permit detailed analysis. Nevertheless, something is known about its properties: The molecules are small molecular weight polypeptides with a cationic charge. Future research efforts will seek to further purify and characterize these substances.

HORMONES FROM LUNG TISSUE

. . . Regulators of Body Functions

For a number of years scientists have known that the lung secreted certain substances, but the precise nature of these substances was unknown. This year two peptide hormones, important regulators of body function, have been discovered and purified from lung tissue. The newly isolated lung peptides have potent and opposite actions on the airways, blood vessels of the lung and systemic circulations, and other organ systems. One peptide relaxes the airways and pulmonary vessels, and the other peptide contracts them. Between these two peptides, therefore, the lung has the potential to modify or regulate some aspects of its own function

—as well as other functions such as systemic blood flow and blood pressure. The peptide that elicits contraction of airways could be an important mediator of asthmatic reactions; the other (relaxant) peptide has possible usefulness as a bronchodilator in the treatment of asthma.

RESPIRATORY DISTRESS SYNDROME

. . . Role of Insulin Clarified by Use of New Lung Assay

Each year, nearly 40,000 babies are born with respiratory distress syndrome (RDS), and many of these die unless they are given prompt treatment. In RDS, the newborn's lungs are immature and are unable to synthesize adequate amounts of surfactant, a substance which reduces the surface tension of pulmonary fluids and so contributes to the elastic properties of lung tissue. For some time, it has been known that infants born to diabetic mothers have an increased incidence of RDS. Investigators have now developed a model system—the cultured fetal rat lung—which facilitates studies to determine the effect of insulin on fetal lung maturation. Results of initial studies indicate that insulin delays morphological maturation in the cultured fetal rat lung, a finding which may explain why RDS is so common in infants born to diabetic mothers. *In utero,* these infants are exposed to high levels of insulin as glucose from the hyperglycemic mother freely crosses the placenta and stimulates the fetal pancreas to produce insulin. This basic understanding presents new opportunities and challenges for developing effective therapies to prevent immature lung development in infants born to diabetic mothers.

BLOOD COAGULATION

. . . Antagonistic Roles of Vitamin K and Coumarin Clarified

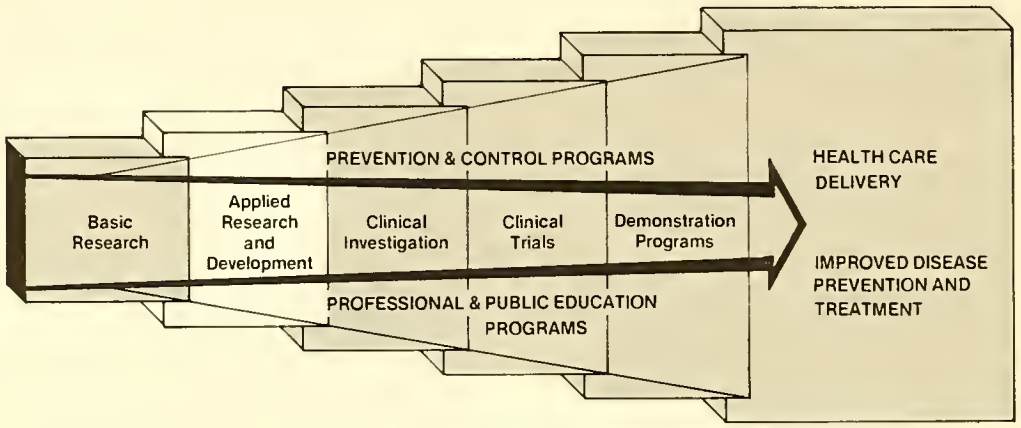
An important development in understanding the action of the clotting system and the roles of vitamin K and coumarin was the discovery of the presence of a new amino acid, gamma carboxyglutamic acid, in human prothrombin. Gamma carboxyglutamic acid must be present for the protein prothrombin to be active in the clotting system. It is now known that vitamin K is essential for the development of gamma carboxyglutamic acid from the glutamic acid residues of prothrombin, whereas coumarin inhibits carboxylation in the synthesis of prothrombin. These discoveries not only contribute to basic knowledge of protein biochemistry and blood clotting but also have important implications for clinical anticoagulant therapy.

BLOOD COAGULATION

. . . Primary Structure of the Prothrombin Molecule Determined

In the past year, a major breakthrough in our understanding of blood coagulation at the molecular level has been made. The complete amino acid sequence of prothrombin has now been determined through studies done on bovine prothrombin. Prothrombin, a protein present in plasma, is converted to thrombin during the coagulation process. Thrombin, in turn, converts fibrinogen (a soluble compound) into fibrin (an insoluble protein) which forms the essential portion of the blood clot. The sequence of the proteolytic cleavages (splitting of the protein) that leads to the production of the active enzyme thrombin has been determined by several groups of investigators. Studies are continuing to elucidate the organizing mechanism of the "prothrombinase complex" (prothrombin, Factor Xa, Factor V, phospholipid, and calcium). It appears that some of the gamma carboxyglutamic acid residues in prothrombin bind specifically to calcium and that this interaction leads to the protein conformation change required for the formation of a prothrombin-phospholipid complex. The nature of the Factor V-binding region of prothrombin is also under investigation, as well as the role of the "pro" fragments released during thrombin formation. Attempts are being made to produce antisera specific for the nonthrombin fragments and for the thrombin portion, in anticipation that such antibodies may provide a sensitive assay for thrombin conversion studies *in vivo*. The complete elucidation of the primary structure of prothrombin represents a basic advance in our understanding of a very complicated process—blood coagulation.

APPLIED RESEARCH AND DEVELOPMENT



Applied research is systematic study directed specifically toward applying new knowledge to meet a recognized need. In both the laboratory and clinical setting, applied research is aimed at obtaining specific knowledge that will enable the investigator to judge whether it is feasible to produce a new or improved means of preventing, diagnosing, or treating a particular disorder. Applied research is dependent upon the existence of a relevant scientific base. It may be targeted to determine whether, with the current knowledge base, a means can be devised to accomplish a specific practical goal.

Development is the systematic application of knowledge toward the production of useful material, devices, agents, and systems or methods to meet a recognized need. It includes design, development, and improvement of prototypes and new processes to meet functional or economic requirements.

An example of applied research and development may help to define better the scope of these activities and their role in the biomedical research spectrum.

For many years it has been postulated that the amount of heart muscle that would undergo irreversible damage in the course of a heart attack was generally not fixed at the onset of the attack. It was believed that significant areas of heart muscle, deprived of adequate blood flow, were in jeopardy, but had not undergone irreversible damage. One of the pressing needs at that time was to test this hypothesis and to develop a means for minimizing damage to the areas in jeopardy. First, however, it was necessary to develop methods for accurately quantifying the extent of heart muscle that had undergone irreversible damage, and for identifying and treating the ischemic but potentially salvageable area.

During the past year, after several years of targeted research by many individuals in a variety of disciplines, methods have been developed to quantify ischemic areas accurately. These diagnostic methods of measurement involve radioimmunoassay of enzymes, radioisotope imaging, computer image enhancement of x-ray, and ultrasound. As a result of this technological progress, meaningful clinical drug studies can now be undertaken to limit the area of damaged tissue. A clinical trial is therefore being initiated to test the efficacy of certain potentially beneficial regimens.

Not only does this advance allow the prospect of better and more effective treatment for those with overt coronary artery disease, but it also has led the way to the development of instrumentation which can, at this time, be employed in earlier preventive stages. This year, modifications of the x-ray imaging technique have been reported. These technical changes make it possible to diagnose exertional coronary insufficiency before a damaging heart attack occurs. Patients shown to be at risk can then be put on a health care regimen that could avert the costly and debilitating effects of myocardial infarction. On

the other hand, individuals with negative tests can be reassured and encouraged to maintain their good health.

CARDIAC PACEMAKERS

. . . Improved Technology

Cardiac pacemakers are a widely used component of medical therapy for a number of cardiac diseases. Continued technological improvements in the pacemakers have been made. These improvements include: development of a rechargeable battery-powered cardiac pacemaker; extension of the life of cardiac pacemakers by developing new and improved electrodes, batteries, and circuits; and refinement of patient treatment and follow-up using electronic and telephonic communication.

AN ADVANCE IN LUNG DISEASE DETECTION

. . . Ventilation-Perfusion Ratios Determined

With the development of a method to determine continuous distributions of ventilation-perfusion ratios (the ratio of ventilation to blood flow), a notable advance has been made in understanding lung gas exchange in healthy and diseased lungs. The complex method includes infusion of six inert gases followed by simultaneous collection of blood samples and mixed expired gas. The technique gives the amount of blood flow to unventilated lung (shunt) and also indicates the approximate amount of blood flow to lung units having specific ventilation-perfusion ratios. In various lung diseases, ventilation-perfusion ratios are not uniform throughout the lung. These ratios change, for example, in conditions such as asthma, respiratory distress syndrome, and interstitial lung disease. Since this technique can determine the continuous distribution of ventilation-perfusion ratios, its potential for detecting the subtle signs of early lung disease is promising.

LUNG AIRWAY CLOSURE

. . . New Method of Detection Developed

Using the fiberoptic bronchoscope, collateral ventilation has been visualized for the first time *in vivo*. For some time, it has been recognized that ventilation can reach lung lobules either directly from the bronchioles or indirectly by way of collateral channels. However, collateral ventilation is now being viewed as an important factor in maintaining gas exchange in normal persons as well as in aiding patients with lung diseases such as chronic bronchitis, emphysema, and asthma which involve obstruction of small airways. In one study of patients with emphysema, collateral ventilation was considerably greater than in normal subjects. In another study in animals, it was shown that when there is failure to sigh, there is a decrease in collateral ventilation and, after a deep breath, there is an increase in collateral ventilation. This finding has clinical implications, suggesting that if patients are encouraged to breathe deeply and cough after anesthesia or surgery, collateral ventilation may be increased and airway closure avoided.

EARLY DIAGNOSIS OF PULMONARY EDEMA

. . . New Noninvasive Procedure

A new and promising method for the diagnosis of pulmonary edema has been developed. Tested in sheep and now being readied for clinical use, this noninvasive technique uses imaging and counting devices to measure the rate of accumulation for a radioactive labeled protein in the lungs. The special importance of the test is that it measures accumulation rates rather than total accumulation, and thus promises to be important in the early diagnosis of pulmonary edema.

HEPATITIS

. . . Progress in Prevention and Detection

Hepatitis is the most common disease transmitted through blood transfusions. The discovery of the serum hepatitis antigen (HBsAg, or Australian antigen) and the demonstration of its relationship to human hepatitis type B have opened the way for studies to develop a vaccine against hepatitis. Recent work has led to the development of a method for purifying hepatitis virus and associated particles. It is anticipated that this method can be applied to large-scale production of the virus, which in turn will permit the preparation of a hepatitis vaccine sufficiently potent and safe for tests in man. This vaccine, currently being developed and tested, could

help diminish the threat of transfusion-transmitted hepatitis B. Further Institute support for research in hepatitis detection has culminated in the characterization of the e antigen. This recently discovered soluble antigen, which appears to be a better marker for infectivity than the Australian antigen, could greatly increase the sensitivity of our detection capability.

PLASMA FRACTIONATION

. . . Cost-Saving New Approach

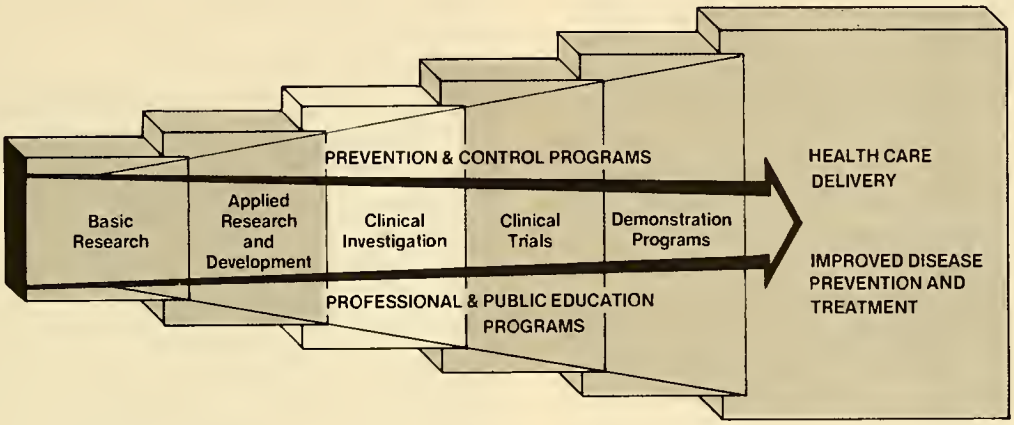
A chromatographic procedure for the purification of Factor VIII, prothrombin complex, albumin, and gamma globulin has been developed. The yield and purity of the fractions it produces are at least equal to those of commercially available plasma fractions. This approach is based on a newer separation principle than that of present commercial fractionation techniques, which are slow and costly. Approximately one week is required to process one batch of blood. Since the major financial outlay is for the initial purchase of the blood, considerable capital is tied up in nonnegotiable inventory. The new chromatographic procedure developed over the past three years is a significant advance in plasma fractionation methodology. It potentially offers a less expensive, more efficient method which can be fully automated and yield high quality products.

SICKLE CELL DISEASE

. . . Progress Toward Prenatal Diagnosis

Recent advances make it possible to diagnose sickle cell disease from fetal blood *in utero*. However, current methods for obtaining fetal blood have considerable risks. Investigators are presently refining a flexible fetoscope in carefully controlled studies with animals (sheep and baboons). With this instrument, it will be possible to obtain fetal blood under direct visualization, thereby increasing the accuracy and safety of the procedure. Prenatal diagnosis will greatly increase the options genetic counselors can offer couples at risk.

CLINICAL INVESTIGATION



Clinical investigation is the vital link between basic research and clinical practice. It translates the results of basic and applied research into potential regimens for disease prevention and treatment. Conversely, clinical observations form the basis for research designed to determine, ultimately, the etiology of disease.

For a number of diseases, there is no known cure. In those instances, clinical investigations, coupled with basic research, are critical to the development of effective therapies to alleviate the symptoms or delay disease progression. For example, the basic defect responsible for sickle cell anemia is known. Nevertheless, therapies to prevent or reverse the debilitating crises do not exist. Furthermore, it is not known why the character and severity of the complications of the disease vary so greatly from individual to individual.

Treatment of sickle cell disease is hampered by lack of information on the natural history of this hemoglobin disorder. Information is particularly lacking on the clinical course of the disease, starting at birth, and criteria need to be developed in order to classify organ involvement and the severity of the disease process.

For these reasons, the Institute initiated, in 1977, a collaborative, clinical investigation of the frequency of occurrence and concurrence of health-related events in the clinical course of patients with sickle cell disease. Prospective longitudinal and cross-sectional studies are directed toward identifying and evaluating the factors which determine the clinical course and the presence or absence of complications. The knowledge gained from this long-term, comprehensive study will greatly increase our ability to predict and treat the complications of this hereditary anemia.

Another example is congenital heart disease. Twenty-five years ago this disease was a major health problem. Since then, significant progress has been made in the diagnosis and surgical treatment of congenital heart lesions. Advances in clinical research have enabled children, infants, and even newborns to be more adequately diagnosed, and consequently treated. Particularly encouraging are recent improvements in echocardiography, a noninvasive technique previously of value only in older children. This method, which makes possible the direct visualization of the spatial location of the chambers and valves of the heart and of the major blood vessels, facilitates determination of which chambers of an infant's heart are enlarged and which valves are malfunctioning. These new techniques allow the monitoring of the effect of medical and surgical treatment on the detected abnormalities. With about 25,000 children born each year with defective hearts, techniques such as this, which make early diagnosis and prompt treatment more accessible, are highly significant.

DIET, THROMBOSIS, AND CORONARY HEART DISEASE

. . . Two New Community Studies

Two important studies have tested the hypothesis that diet is associated with the development of thrombosis and coronary heart disease. A collaborative pilot study supported by the NHLBI and the USDA was conducted to test the hypothesis that diets high in saturated fat influence the fatty acid composition of platelet membrane phospholipids causing greater aggregability of the platelets. Platelet aggregation is considered by some to be an essential step in the development of a clot or thrombus. In three carefully selected population groups, preliminary results indicate that differences in the fatty acid composition of the blood platelets generally reflected the composition of fat in the diets. Significant increases were noted in the platelet aggregation tests of the population group which consumed the highest percentage of dietary saturated fatty acids.

A large epidemiological study investigating the correlation between diet and serum cholesterol has collected dietary intake data on more than 8,000 men in Puerto Rico. In an urban study group, there was a positive association between both serum cholesterol levels and body weight and dietary intake of cholesterol, percentage of calories from fat, and percentage of calories from saturated fatty acids. Negative associations were found between serum cholesterol levels and percentage of calories from carbohydrates. The demonstration of statistically significant associations between dietary variables and serum lipid levels within a single population adds important new information concerning the role of diet in coronary heart disease.

HIGH BLOOD PRESSURE

. . . A Potential Biochemical Marker

Because in many cases high blood pressure (hypertension) is asymptomatic, identification of actual or potential hypertensives is difficult. Early studies showed that adults with essential hypertension had lower urinary kallikrein excretion than a comparable group of adults with normal blood pressure readings. In a new study, urinary kallikrein excretion has been measured in both black and white children, 5 to 18 years of age, whose families have a number of members with high blood pressure. Measurements of the children's family members were also taken. Families with lowest mean kallikrein concentrations tended to have higher blood pressure readings than families with higher kallikrein concentrations. In addition, urinary kallikrein concentration was found to be significantly lower in black children than it was in white children. This correlates with the high incidence of hypertension known to occur in black adults. While this study does not clearly involve kallikrein in the pathogenesis of essential hypertension, it nevertheless suggests a potential relationship between a biochemical marker and blood pressure—a correlation that holds promise for developing screening methods for early identification of potential hypertensives.

SUDDEN CARDIAC DEATH

. . . Results of Postmortem Study

A recent analysis of findings from postmortem examinations of victims of sudden cardiac death demonstrates that the causes and process of sudden cardiac death are much more complex than was anticipated. Most of the individuals examined had significant coronary heart disease (75 percent or more reduction in one or more major arteries), yet 8 percent of the cases showed no significant vessel disease. There was also a lack of correlation of age with either severity of artery disease or with previous infarction as ascertained by history or examination. Although acute thrombosis and recent myocardial infarction were found in 5 percent to 10 percent of the cases, respectively, this is an insufficient frequency to be considered causally related. On the other hand, 76 percent of the cases showed selective myocardial necrosis (tissue death) which antedated the sudden cardiac event. The significance of this process of cell injury is not known, but it was observed both in cases with and without coronary artery disease, and may be etiologically related. Postmortem angiograms of 39 percent of the victims were compared with coronary angiograms of a number of survivors. Vessel disease was found to be no more severe in the victims than in the survivors, suggesting that factors in addition to the severity of artery disease may be the immediate precursors of sudden cardiac death. These findings illustrate the

complexities surrounding a better understanding of the genesis of sudden cardiac death and indicate that much more work needs to be done.

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

. . . Advances in Basic Understanding and Prophylactic Treatment

Low doses of the anticlotting agent heparin, given before and after surgery, can reduce significantly the incidence of deep-vein thrombosis (clotting) and pulmonary embolism. Each year in the United States, 5 million individuals over age 40 undergo major general surgery. Of these, one or two out of each 1,000 die postoperatively from pulmonary embolism. Controlled clinical trials have shown that low-dose heparin is effective in reducing the incidence of deep-vein thrombosis which leads to pulmonary embolism. However, appropriate situations and proper doses must be chosen to avoid excessive bleeding during surgery. Further development of this and other clinically useful hemostatic therapies will be facilitated by an increased understanding of the regulation of the coagulation scheme. A major question has been, what in the natural process prevents clotting blood from clotting completely? Recent basic and clinical research suggests that the system is modulated by inhibitors, the most important of which is antithrombin III. Studies at the Specialized Centers of Research clarified that heparin is bound to antithrombin III by electrical charges and selectively activates it to regulate its anticoagulant effect. This line of research is fundamental to the development of low-dose heparin therapy to prevent deep-vein thrombosis and pulmonary embolism and to an understanding of the basic mechanism underlying the action of heparin.

PERIPHERAL VASCULAR DISEASE

. . . Improved Diagnosis

Recently, a more accurate diagnostic procedure for detecting small venous clots has been developed. Production of a specific antibody to fibrinopeptide fragments released from fibrinogen in the presence of thrombin now enables clinicians to detect these circulating fragments, which are indicators of clot formation, by radioimmunoassay. Use of this new method could greatly assist clinicians to more accurately determine the existence and location of a deep-vein thrombus. Use of the radioimmunological method to measure fragments of other proteins active in the coagulation process could be of considerable diagnostic significance.

CONGENITAL HEART ABNORMALITY

. . . Possible Alternative to Surgical Repair

Patent ductus arteriosus is a persistence after birth of the normal fetal vascular channel between the pulmonary artery and the aorta. In full-term infants, this channel gradually closes off during the first few weeks of life. In some infants, however, the ductus often remains open, and blood is shunted from the pulmonary artery to the aorta, bypassing the lung and causing the infant to be cyanotic. Preliminary trials in animals have demonstrated that administration of prostaglandin-inhibiting drugs (like aspirin and indomethacin) results in closure of the ductus. The potential ramifications of this treatment, however, are unknown, and until more information is available, this therapy will remain an issue of controversy. Additional studies are continuing to determine whether the administration of prostaglandin-inhibiting drugs to such infants is a safe and effective alternative to surgical closure of the ductus.

In newborns with certain forms of serious congenital heart disease, life depends upon the continued flow of blood through the ductus. In these cases, prostaglandins themselves are being used to keep the ductus open until surgical correction of the heart defect is possible.

ASPIRIN-INDUCED ASTHMATIC ATTACKS

. . . Mode of Action Clarified

The mechanisms underlying aspirin-induced bronchospasms in certain sensitive individuals are not understood. While in some patients hypersensitivity reactions involving antibodies may explain this phenomenon, it appears that in a large majority of aspirin-intolerant individuals immunologic mechanisms may not play a prominent role. In such cases, aspirin-induced asthma may represent a model for the non-allergic form of this reversible airway disease.

Prostaglandins play a role in the control of bronchial muscle tone. Recent data indicate that irritation of the bronchus with aspirin in aspirin-sensitive individuals produces changes in serum prostaglandin levels. This might be explained by the finding that aspirin and aspirin-like compounds are potent inhibitors of prostaglandin synthesis.

If it can be demonstrated that aspirin induces asthma through its ability to alter prostaglandin metabolism, pharmacologic manipulation of prostaglandin levels might be helpful in preventing or reversing the bronchospasm in individuals following aspirin ingestion.

SICKLE CELL ANEMIA TREATMENT

. . . Studies of Anti-Sickling Agents

Of all the anti-sickling drugs investigated, cyanate has been the most promising. *In vitro* studies of the effect of cyanate on sickling have demonstrated that it most likely increases the oxygen affinity of hemoglobin S (sickle hemoglobin), thus preventing deoxygenation and the consequent hemoglobin aggregation and red cell sickling. Since studies to date show that oral administration is toxic, techniques are being developed to administer cyanate by extracorporeal methods. Some of the patient's blood is withdrawn and treated with cyanate and then reinfused into the patient after the free cyanate has been removed. Preliminary data indicate that this treatment can reduce the severity of anemia and the frequency of crises without causing significant side effects.

BLOOD PLATELETS

. . . Progress in Transfusing Sensitized Patients and Storing Platelets

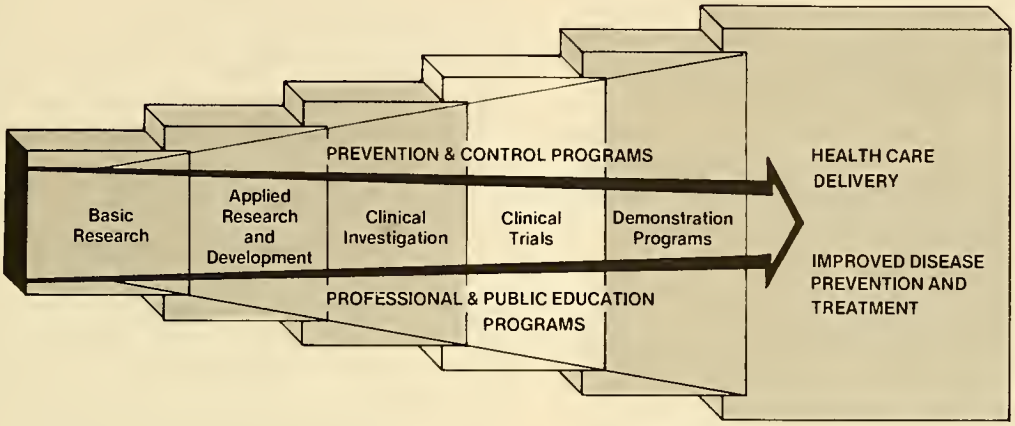
Blood platelets play a prominent role in the initiation of coagulation and in the maintenance of blood vessel integrity. Leukemia patients often have low platelet levels either as a direct result of the disease or as a toxic reaction to the drugs used in treating the disease. Consequently, these patients and others with low platelet levels due to a platelet abnormality or drug therapy require frequent platelet transfusions to prevent serious hemorrhaging. Multiple platelet transfusions can, however, stimulate an allergic reaction as a result of sensitization to the histocompatibility (HLA) antigens transfused. Findings from a number of recent studies indicate that matching donor and recipient for HLA antigens is feasible on a large scale and may be beneficial in platelet transfusions of highly sensitized patients. One limitation, however, is the short shelf life of platelets. Therefore, widespread clinical application of this advance is dependent upon the development of improved techniques to preserve and store platelets. Studies involving short-term preservation have recently defined optimal liquid-state storage to be three days. Investigations of long-term preservation by freezing are in progress, and preliminary results suggest that frozen platelets can be stored for about six months without losing their hemostatic effectiveness. This increased capability to store platelets greatly enhances our ability to successfully treat patients requiring frequent platelet transfusions and to provide sensitized patients with platelets matched for HLA antigens.

KIDNEY TRANSPLANTATION

. . . Better Understanding of Graft Rejection

Kidney transplantation has become a standard treatment for chronic kidney failure. Graft rejection, however, remains a problem. Recent discoveries have demonstrated that matching for transplantation antigens (HLA) is not the only important factor in ensuring success of a kidney transplant. We are now able to separate out T and B lymphocyte cells and the serum for typing B cells has been developed. B cells have surface antigens that under certain circumstances produce antibodies that may be responsible for stimulating T cells to become the cells responsible for delayed graft rejection of kidney transplants. In some patients the formation of "block" antibodies protects the graft against cytotoxic antibodies and the lymphocyte cells responsible for delayed graft rejection. Discovery of the mechanism to induce production of blocking antibodies in all patients presents a possible solution to kidney graft rejection.

CLINICAL TRIALS



Clinical trials test, in a carefully controlled setting, the efficacy and safety of preventive and therapeutic regimens with the potential to save hundreds of thousands of lives and billions of dollars each year.

The objective of the large-scale clinical trial—a critical activity in the biomedical research spectrum—is to acquire information regarding the effect of a given form of medical or surgical intervention. Randomized clinical trials are used to evaluate new drugs, devices, or surgical techniques; compare alternative patient management modes; determine the effectiveness of different treatments; or measure the efficacy of intervention programs for high-risk populations. Trial results facilitate the projection of potential consequences of successful intervention—risk reductions, changes in longevity, morbidity, and mortality, and economic savings.

The clinical trial is a key step in the long, difficult, and complex process which converts research findings to clinically applicable prevention or treatment regimens. Trials depend on a strong scientific base to develop and refine regimens to be tested. The decision that the base of knowledge concerning a specific prevention or therapeutic regimen is sufficient to warrant initiation of a formal clinical trial puts in motion a series of steps, each of which requires time, effort, and resources:

- Definition of the questions to be addressed by the trial.
- Design of a valid, carefully controlled trial to answer those questions.
- Justification of the trial in terms of feasibility and in terms of medical, economic, social, and ethical implications.
- Identification of clinical centers qualified to participate in the trial.
- Establishment of a collaborative network of such clinics fully committed to follow a common protocol, adhere to trial standards, and complete and submit required reports.
- Implementation—initiation, coordination, and monitoring—of the trial itself.
- Development of reliable data on the questions posed by the trial.
- Validation and analysis of all trial data and reporting of results.
- Dissemination of results to the scientific and health care communities and to the public.

The time involved in such an undertaking is years—anywhere from two to 10 depending on the size and complexity of the trial. Its successful completion will involve the concerted effort of hundreds of scientists, clinicians, analysts, and support personnel. And the cost can reach tens of millions of dollars by the time a trial is completed and its results disseminated. Therefore, the decision to undertake a clinical trial is not made without considerable

deliberation. Most often, a small pilot clinical trial is used to determine the feasibility of and gains to be expected from a larger trial. As an example, findings of a pilot study to investigate the use of aspirin therapy to reduce the incidence of recurrent myocardial infarction suggested that such a trial was feasible, and, in fact, that aspirin ingestion might significantly reduce the incidence of reinfarctions. As a result, a large-scale clinical trial was initiated.

In another instance, however, examination of the results of a pilot clinical trial to determine the potential benefits of treating persons with mild hypertension led in part to the decision that a full-scale clinical trial, while important, could not be carried out at this time.

The following examples of clinical trials now under way or recently completed emphasize the importance of this activity to the nation's health and the interrelationships among the various activities in the biomedical research spectrum.

- **The Multiple Risk Factor Intervention Trial.** Epidemiological studies have shown that the simultaneous presence of multiple cardiovascular risk factors elevates risk more than would be expected from consideration of the individual risk factors alone. The Multiple Risk Factor Intervention Trial is a long-term study to determine whether lowering three major factors simultaneously—high levels of cholesterol in the blood, high blood pressure, and smoking—has a significant effect on cardiovascular morbidity and mortality. The study is evaluating treatment and risk-reduction methods that may be applicable to the population at large. Over 365,000 people were screened to identify the 12,000 high-risk subjects involved in the study.
- **Coronary Primary Prevention Trial.** This trial, a double-blind study involving some 4,000 patients for seven years, is testing the hypothesis that long-term reduction of serum cholesterol in men with elevated cholesterol levels (but initially free of coronary heart disease) will lead to a lowered incidence of coronary heart disease. The study emanates from the Institute's Lipid Research Clinics, which carry out fundamental and applied research and epidemiologic studies of lipids and lipoproteins. Because arteriosclerosis is so intimately tied to clinical risk of coronary heart disease and because increased lipid levels are highly correlated with both arteriosclerosis and coronary heart disease, the study will provide significant data which could greatly facilitate the development of measures for preventing heart disease.
- **Hypertension Detection and Follow-up Program.** While clinical research has demonstrated that appropriate therapy, in controlled clinical settings, can reduce morbidity and mortality in men with diastolic blood pressures above 105 mm Hg, it is not known whether antihypertensive therapy, applied to hypertensives in the general population and making use of existing medical resources, can significantly reduce morbidity and mortality. The Institute therefore initiated a controlled, cooperative clinical trial, involving 14 clinics and 11,000 patients, to determine: (1) those significant operational, socioeconomic, and motivational or behavioral factors which would influence the acceptance of antihypertensive therapy in a defined population; and (2) whether a practical intensive antihypertensive program can significantly reduce morbidity and mortality in a representative sample of hypertensives in the general population or in selected population groups. The trial has great significance as both a test of methods to effect hypertension reduction as well as a test of the effectiveness of such reductions on lowering morbidity and mortality.
- **Aspirin Myocardial Infarction Study.** The primary objective of this collaborative clinical trial is to determine whether the administration of one gram of aspirin a day to men and women who have had at least one documented myocardial infarction will result in a significant reduction in total mortality over a three-year period. A total of 4,200 patients have been enrolled in this study during the one-year recruitment period. They are between the ages of 30 and 70; at the time of

recruitment, they were no closer than 8 weeks and no farther than 5 years from their most recent myocardial infarction; and they did not suffer from ulcer symptoms or aspirin intolerance. Thirty clinical centers, a coordinating center, a central laboratory, and an ECG center are collaborating on this trial.

- **Coronary Artery Surgery Study.** This large-scale collaborative trial is comparing the effects of coronary artery bypass surgery with those of non-surgical treatment on the morbidity and mortality of patients with chronic coronary heart disease. Approximately 17,000 patients are enrolled in the study registry. This resource will eventually number 20,000, and 700 to 900 patients will participate in the randomized trial itself. Sixteen clinical centers are collaborating in this study, and an ECG laboratory has been established to assure uniform and accurate use of this procedure. A major benefit of this study will be the analysis, preparation, and publication of "non-endpoint data" (data other than death and myocardial infarction) in the registry patients. This will include studies of complications involving coronary angiography, correlations between results of exercise testing and findings on angiography, and analysis of risk factors for coronary artery disease correlated with results of angiography.

- **Neonatal Respiratory Distress Syndrome Prevention Trial.** Neonatal respiratory distress syndrome (hyaline membrane disease), the single most frequent cause of death of newborn infants, is responsible for the death of an estimated 12,000 newborn infants annually. In 1976, the Institute initiated a collaborative, double-blind clinical trial involving five clinical centers and 600 patients to evaluate the efficacy and safety of antenatal steroid therapy as a means of preventing hyaline membrane disease. This study is assessing the prophylactic effectiveness of administering steroid 24 to 72 hours prior to parturition, and the frequency and severity of short- and long-term side effects associated with the treatment. If the treatment is demonstrated to be safe and effective, the impact on morbidity and mortality of newborn infants will be significant.

Following are selected 1977 highlights of the Institute's major clinical trial programs.

LIPID RESEARCH CLINICS PROGRAM

. . . Results of Studies Now Available

To date, about 60,000 subjects have been screened in the Lipid Research Clinics Program (LRC). Results which can now be reported for the first time provide population-based distributions for cholesterol and triglyceride levels. Analysis indicates a significant drop in serum cholesterol levels in certain segments of the U.S. population.

The pediatric study of approximately 20,000 subjects, newborn to 19 years old, has shown that during adolescence there is a decline in plasma cholesterol levels. Further research is required to establish the cause for this decline and elucidate the factors that control plasma cholesterol levels. Blood lipid levels in children are attracting increasing attention as it is recognized that many factors determining atherosclerosis are probably developed in childhood.

Analysis of diet suggests that in the United States, people are now consuming less cholesterol and saturated fats and more polyunsaturated fats than previously. These findings are consistent with other measures of U.S. food consumption and, if confirmed, could explain in part the modest blood cholesterol reductions and significant reduction in coronary mortality that have occurred.

In the LRC studies, slightly but significantly lower levels of blood lipids were observed in subjects in higher educational or socioeconomic categories. These findings are consonant with reports that such groups are also reducing other coronary risk factors such as cigarette smoking and uncontrolled high blood pressure, and most likely reflect an improved awareness of coronary disease risk factors and the means to reduce or eliminate them.

Now that the study groups have been established and data on their blood lipid and lipoproteins collected, it is possible to initiate further research to clarify the correlation between blood lipid levels

and risk of heart attack. Recent epidemiological studies suggest that the level of high density lipoprotein (HDL) correlates inversely with heart attack and heart attack death. This finding could open the way to developing new approaches to therapy. It also highlights the need for more basic research on the structure and function of HDL.

BETA-BLOCKING AGENTS IN HEART ATTACK SURVIVORS

. . . Initiation of a Clinical Trial

In 1977, the NHLBI initiated a major clinical trial designed to determine if the regular administration of propranolol (a beta-blocking agent) to people who have had at least one documented heart attack will result in a significant reduction in mortality over a three-year period. A total of 4,200 individuals within approximately two weeks of having had a heart attack will be involved in this double-blind trial; one-half of these will be randomly assigned to propranolol, one-half to a placebo. Beta-blocking agents have proved effective in conditions such as hypertension and angina pectoris. This trial will test the hypothesis that their properties—including anti-arrhythmic effects—are beneficial to survivors of heart attacks.

EVALUATION OF TREATMENT FOR UNSTABLE ANGINA PECTORIS

. . . Surgery Versus Medical Therapy

Initiated in 1972 and currently in the data analysis phase, a cooperative trial involving eight institutions is comparing the effectiveness of medical and surgical therapies in the management of acute stages of unstable angina pectoris. Findings indicate that patients with unstable angina may be safely treated with intensive pharmacological therapy, individuals with persistent pain may be studied by coronary angiography, and those with left main coronary artery obstruction and continued intractable pain may require surgery. Prophylactic surgery to prevent a myocardial infarction or death is not otherwise indicated.

The finding that medical and surgical therapy are equally effective for certain categories of patients is significant in terms of potential economic savings realized through selection of medical treatment. From 50,000 to 70,000 heart operations are performed annually at a cost of $10,000 to $20,000 each. Eliminating even a small percentage of these operations would mean a significant reduction in national health care expenditures on an annual basis.

HIGH BLOOD PRESSURE TREATMENT

. . . Effectiveness of Propranolol Evaluated

Over the years, a number of studies have tested the effectiveness of combinations of the three commonly used antihypertensive drugs: hydrochlorothiazide, reserpine, and hydralazine. This year, findings of an 18-month clinical trial to study the effectiveness of the antihypertensive agent propranolol were published. Jointly sponsored by the Veterans Administration and NHLBI, the double-blind, placebo-controlled trial on 450 male patients with mild essential hypertension revealed that propranolol alone and propranolol plus hydralazine were less effective than the standard regimen of reserpine plus hydrochlorothiazide in achieving and maintaining reduced blood pressure. Propranolol was introduced more than a decade ago as an effective agent in the treatment of hypertension, and its proponents maintain that patients on propranolol are relatively free from the disturbing side effects of lethargy, nasal stuffiness, depression, and impotence sometimes associated with reserpine therapy. In this study, however, there was no significant difference in the side effects either spontaneously reported by, or elicited from, patients. Further disadvantages of propranolol therapy as compared with reserpine therapy were noted: it requires adjustment of the dosage until maximum results are obtained; it is considerably more expensive; and it requires more frequent dosages per day.

Findings of the clinical trial did show propranolol to be as effective as standard regimens, however, when combined with hydrochlorothiazide and when combined with hydralazine and hydrochlorothiazide. While the mechanisms of the antihypertensive effects of thiazides have not been completely clarified, it appears that thiazides, by reducing the volume of extracellular fluid, play an important role in enhancing the effects of antihypertensive agents.

IMPROVED MANAGEMENT OF BACTERIAL INFECTION IN INFANTS

. . . Prevention of Infection

Bacterial infection is a significant cause of illness and a contributory cause of death in neonates with respiratory distress syndrome (RDS). Such infection has been difficult to manage and often does not respond to antibiotics. Recent preliminary findings have suggested that the presence of normal bacterial flora can provide an effective host defense mechanism against harmful bacteria. A small pilot study has indicated that colonization of infants with a carefully selected non-virulent strain of alpha-streptococci can be done with minimal risk and is very successful in preventing serious infections. As a result of this study, a controlled trial is now under way to determine the efficacy of this method. Infants in this trial will be followed for a year. If the procedure proves effective, it will be a major advance toward prevention and control of one of the primary causes of morbidity and mortality in infants with respiratory distress syndrome.

THE USE OF EXTRACORPOREAL MEMBRANE OXYGENATORS IN PATIENTS WITH ACUTE RESPIRATORY FAILURE

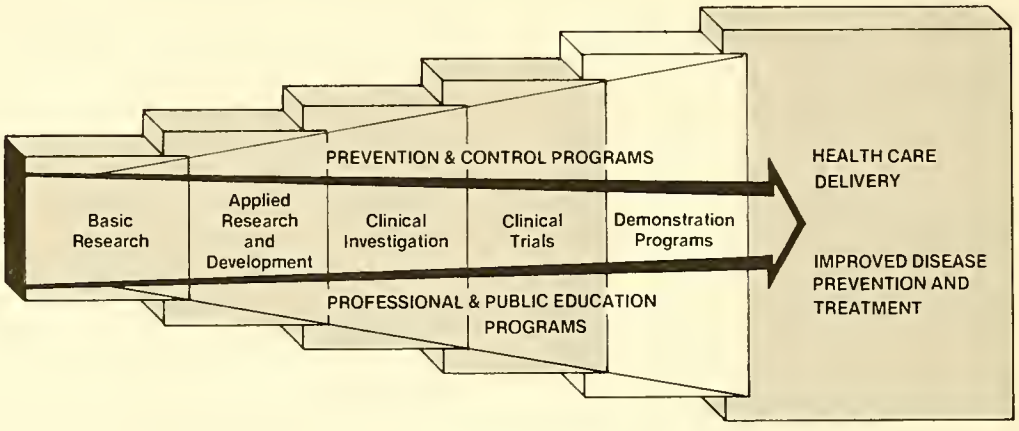
. . . Results of a Clinical Trial

Acute respiratory failure, characterized by the inability to oxygenate the blood, is often seen in young, previously healthy adults and is usually fatal. It is associated with a large number of diverse conditions, usually severe illnesses requiring hospitalization. Some of the conditions that may lead to acute respiratory failure include hemorrhagic or septic shock, severe chest or general body injury, severe viral pneumonia, drug overdoses, inhalation or aspiration of corrosive chemical substances, and widespread fat emboli.

A major clinical trial to evaluate the use of the extracorporeal membrane oxygenator (ECMO) for the treatment of patients with acute respiratory failure has been completed. The trial, begun in 1973 and completed in 1977, involved 831 patients. Ninety of the 831 patients were randomized into two subgroups. The first group received conventional treatment; the second group received conventional treatment and ECMO care. Another 741 patients were followed to assess the natural history of adult respiratory distress syndrome. Results show that ECMO fails to increase survival rates over those achieved with conventional care. The lung pathology data from the study showed that ECMO support did not alter the irreversible damage to the lung associated with acute respiratory failure.

This clinical trial illustrates the value of evaluating new therapies before they are promoted for general use. Although the results of the study discourage promotion of ECMO, they point the way to new approaches to the problem of acute respiratory failure: Significant advances in the recognition and treatment of these patients will only come from multidisciplinary research into the mechanisms of lung injury and repair.

DEMONSTRATION PROGRAMS



Demonstration programs assist in the translation of proven preventive and therapeutic regimens to health practice by testing methods of introducing or enabling the delivery of health care advances to the public. A relatively recent addition to the Institute's programs, demonstration activities have grown from the need to translate research results effectively and efficiently into practice. Such programs will be of even greater importance as the several large clinical trials now under way provide clinically applicable information.

Examples of ongoing NHLBI-supported demonstration programs include the following:

- **National High Blood Pressure Education Program (NHBPEP).** Initiated in 1972, this program aims at increasing physician and health professional awareness and public awareness about both the risks associated with untreated hypertension and the opportunities for effective treatment. The NHBPEP has worked with a large number of communities, state and local health departments, industry, and professional and voluntary health associations. And it has been successful. For example, the number of physician visits for the treatment of high blood pressure has increased over 50 percent, and the number of hypertensives whose blood pressure has been brought to normal through the use of medicine has increased over 100 percent in the last five years.
- **National Research and Demonstration Centers (NRDC).** The National Research and Demonstration Centers program was established in 1975 to respond to the need for a mechanism designed specifically to integrate and coordinate a broad range of research, education, and demonstration activities targeted on a particular disease. NRDCs bridge the gap between fundamental research and the application of research results in health care and in disease prevention. Three centers are now in existence.
  - The *cardiovascular NRDC* focuses on heart and blood vessel diseases, particularly arteriosclerosis. Accomplishments include a community program, demonstrating and evaluating the effect of certain dietary changes on the blood lipids of normal volunteers, which has shown that serum cholesterol can be effectively lowered in this group. In addition, a demonstration and control program developing strategies for countering the influences that lead to smoking in junior high schools has shown evidence of a 50 percent reduction in smoking behavior among seventh graders as a result of study activities.

- The *pulmonary NRDC* conducts research, demonstration, and education projects with special emphasis on occupational pulmonary diseases resulting from prolonged exposure to harmful dust and fumes in various industries and occupations. The center has developed a computer-assisted evaluation system to aid in the preoperative identification of patients likely to have respiratory problems during and following surgery. A program encouraging physicians to use blood gas analysis as a diagnostic and monitoring tool, allows physicians to call blood gas measurements of their patients into a central data center for rapid interpretation.
- The *blood resources NRDC* is mainly concerned with improvement of procedures for the acquisition, processing, storage, distribution, and clinical use of blood and blood products. Demonstration projects in blood banking are increasing blood resources through development of education and recruitment programs for volunteer donors, encouraging hospitals and clinics to use blood fractions as required by the clinical situation rather than transfusing whole blood, and providing training and education for laboratory technicians, medical students, and physicians in the community.

- **Sickle Cell Disease.** The NHLBI program of Comprehensive Sickle Cell Centers facilitates the translation and application of the results of basic and clinical research on sickle cell disease to improved health care at the community level. Education and counseling programs, designed to disseminate accurate information and foster a better understanding by the public, constitute a significant part of the service and demonstration activities of the various comprehensive centers.

  Three centers have developed school curricula for educating students about sickle cell trait and disease. One of these curricula, implemented in intermediate and junior high grade levels, is innovative because it integrates sickle cell information into the normal sequence of courses concerning genetics, biology, physiology, and general health. Counseling programs provide effective communication with individuals found to have abnormal hemoglobin with special emphasis on sickle cell anemia and sickle cell variants. In the area of professional education, Comprehensive Sickle Cell Centers provide current and accurate medical information about hemoglobinopathies to health professionals as a means of improving diagnosis and care and facilitating the translation of research findings to clinical application.

Following are selected 1977 highlights of Institute-supported demonstration programs.

MYOCARDIAL INFARCTION PATIENTS

. . . Benefits of Early Hospital Discharge

Certain patients with uncomplicated acute myocardial infarction are being discharged as early as seven days after admission. In a program testing the feasibility of early hospital discharge, preliminary analyses indicate that in one group of patients the average hospital stay has been halved, from 17 to 8.5 days. This has led to a saving of approximately $1,000 per patient as compared with patients discharged on or after day 10. There has been no increase in morbidity or mortality among these patients during the post-discharge period. These results suggest that early hospital discharge of uncomplicated myocardial infarction patients is clinically feasible and will lead to significant hospital cost savings. Even more impressive are the results of other studies suggesting that early ambulation and discharge of patients with uncomplicated myocardial infarction speed up and enhance the total rehabilitation process.

CONTROL OF HIGH BLOOD PRESSURE IN THE WORK SETTING

. . . A New Effort to Reduce Risk of Coronary Heart Disease and Stroke

Employers as well as employees have a large stake in the control of high blood pressure. Over the past several decades, business has invested millions of dollars and made progress in reducing industrial hazards and accidents. But for every em-

ployee dying from these problems, more than 50 die from cardiovascular disease. Economic costs are staggering; less measurable but still sizable are the costs associated with lost management skills, retraining, and labor turnover. Of the 85 million employed Americans, over 10 percent are known to suffer from high blood pressure or some form of cardiovascular disease. As many as 15 million (20 percent) of the working force may be at risk of cerebrovascular disease due to elevated blood pressure.

In the fall of 1976, the Secretary of Health, Education, and Welfare convened a Conference on High Blood Pressure in the Work Setting. Participants expressed wide interest and support for new initiatives to explore approaches to blood pressure control in the work setting. As a result, the Institute is contracting with worksites to develop demonstration models and with Blue Cross, a third-party payer, to develop model control programs in worksites.

It is anticipated this approach will reach workers, particularly men, who ignore the problem. It is also hoped that, as a result of these programs, rising costs of industrial health benefits will be reduced through prevention programs, underused occupational health programs will be effectively regenerated, and the major problem in hypertension control —lifelong maintenance of therapy—will be impacted significantly through regular reinforcement and monitoring.

CHILDREN WITH ASTHMA

. . . Testing a Self-Management Concept

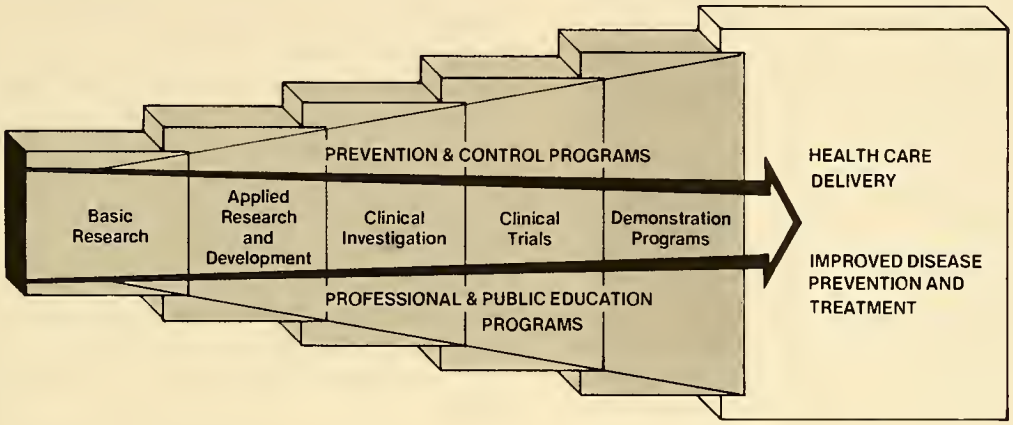
Asthma, a major chronic disease of childhood, may be effectively controlled through appropriate patient behavior. Several centers are testing the validity of the concept that children with asthma can learn to identify and solve their own health problems by avoiding risk and controlling bronchospasm through early and appropriate medication. There is an increasing amount of behavioral research concerning the origins of children's health perceptions, beliefs, and behaviors. This demonstration program will assess these beliefs and behaviors in a population of children with asthma; attempt to influence these children to change the beliefs and behaviors that are unsupportive of the self-management concept; and assess the impact of improved behaviors on the health of children with bronchospasm, on frequency of school absenteeism, and on the utilization of health care facilities.

SMOKING AND LUNG DISEASE

. . . Identification of Presymptomatic Patients

Pulmonary function tests are probably more useful than symptoms in detecting a smoker's risk of developing chronic obstructive pulmonary diseases (COPD). A collaborative demonstration program in three centers has shown that there is a definite relationship between smoking and lung function abnormality, the most impaired lung function being observed in the heaviest smokers. On the other hand, no relationship was found between the presence of respiratory symptoms and abnormal pulmonary function. Reduction of the smoking habit as well as smoking cessation resulted in improvement in pulmonary function, while no improvement was found in subjects who failed to reduce their consumption by more than 25 percent. The improvement in pulmonary function was not influenced significantly by the age or sex of the subjects, although for those under 40 years, women appeared to improve more than men. These findings suggest that symptoms cannot be used to detect smokers who are likely to have lung function abnormalities suggestive of mild peripheral airway obstruction. Pulmonary function tests are therefore recommended.

PREVENTION AND TREATMENT



Clearly, the focus of the biomedical research spectrum—shown by the direction of the arrow in the diagram above—is improved prevention and treatment of the cardiovascular, pulmonary, and blood diseases which comprise the Institute's mandates.

During 1977, several advances resulting from activities along the above spectrum emerged as potential improvements in the prevention and treatment of disease. Following are brief descriptions of these advances.

PEDIATRIC HYPERTENSION

. . . Research Results Translated into Medical Care Guidelines

Up to this time, there has been a wide divergence of opinion and practice regarding ranges and treatment for children's blood pressure. Taking data from studies conducted at the Specialized Centers of Research (SCORs), the Task Force on Blood Pressure Control in Children established ranges of blood pressure in children by age and sex. Charts were developed by the Task Force which allow the practitioner to plot an individual patient's blood pressure over time and compare it with that of his peers. The report also contains recommendations on detection, referral, follow-up surveillance, and treatment. It recommends that blood pressure control for children be a part of their total health care and not a separate screening and detection effort. Members of the task force represented a broad range of professionals who both treat children and are involved in policy planning for health care delivery for children.

PRESERVATION OF RED BLOOD CELLS

. . . New Additive Extends Shelf Life

Currently, red blood cells have a shelf life of only 21 days. Recent studies on the use of adenine as a supplement to red cell preservation solutions were presented at a workshop jointly sponsored by the Institute and the FDA's Bureau of Biologic's Panel on Review of Blood and Blood Derivatives. The workshop concluded with a recommendation to the panel that adenine be licensed as an additive to extend the outdating period of stored red blood cells from 21 to 35 days. As a result, the FDA has moved to license its use. The impact of this action will be reflected in a better product at the old outdating period of 21 days and an opportunity for better inventory management as a result of extending the outdating period.

BLOOD RESOURCES

. . . Implementation of the National Blood Policy

In 1973, the National Blood Policy was issued by the Secretary of Health, Education, and Welfare in response to widely shared perceptions of deficiencies in the blood services provided to the Ameri-

can people by the private sector. The policy established four principal goals: adequacy of supply, high standards of quality, universal accessibility regardless of ability to pay, and efficient collection and utilization of blood and blood products. The American Blood Commission (ABC) was created to implement the goals of the National Blood Policy. Not only has the Institute supported the research of the ABC's task forces, but much of the Institute's blood resources research program is applicable to the goals of the National Blood Policy, which include the establishment of an all-volunteer regionalized blood bank system and movement toward an all-volunteer donor system. To date, several basic studies to analyze our current system have been completed, and the organization of a network of regionalized centers has been initiated. Regulation of blood banks has become much more encompassing and stringent. A systematic assessment of the needs of a national blood data system to monitor blood resources, needs, and costs has also been initiated. A degree of consensus with the blood services complex has been achieved through the efforts of the ABC. Significant technological advances have been made in blood safety, storage, and preservation and in the fractionation of blood components and products. Many problems remain, but the prospects that they will be solved are good. Two major factors—awareness and involvement of the public—though difficult to measure, seem to have increased substantially.

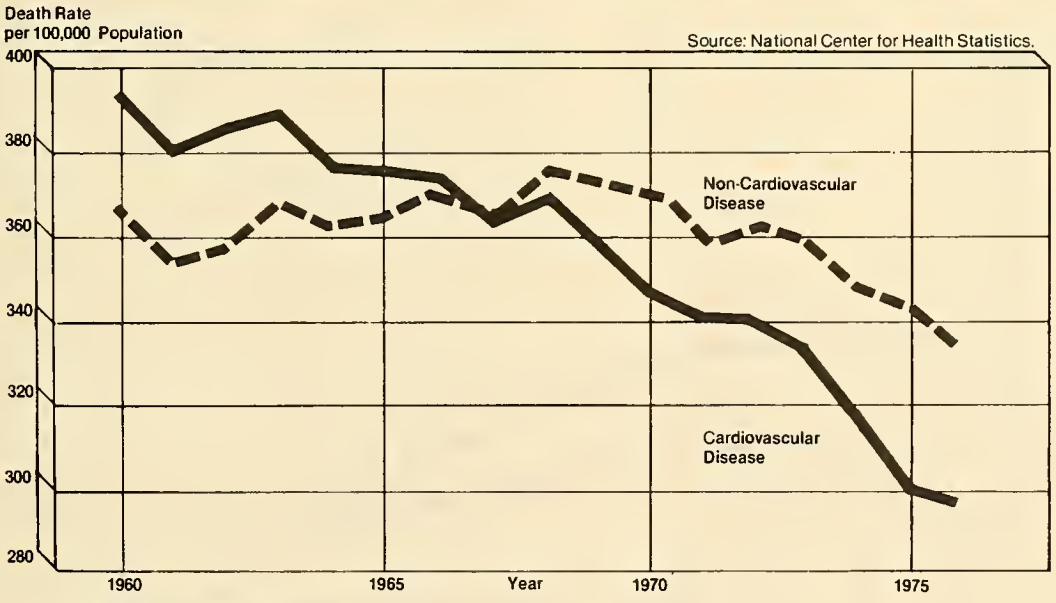
3. INDICATIONS OF PROGRESS AND THE TASK AHEAD

IMPACTS ON MORBIDITY AND MORTALITY

There is good reason to believe that the program strategy represented by the spectrum of activities in Figure 2 can be successful in reducing the morbidity and mortality due to cardiovascular, pulmonary, and blood diseases and thus increase the health and longevity of all Americans.

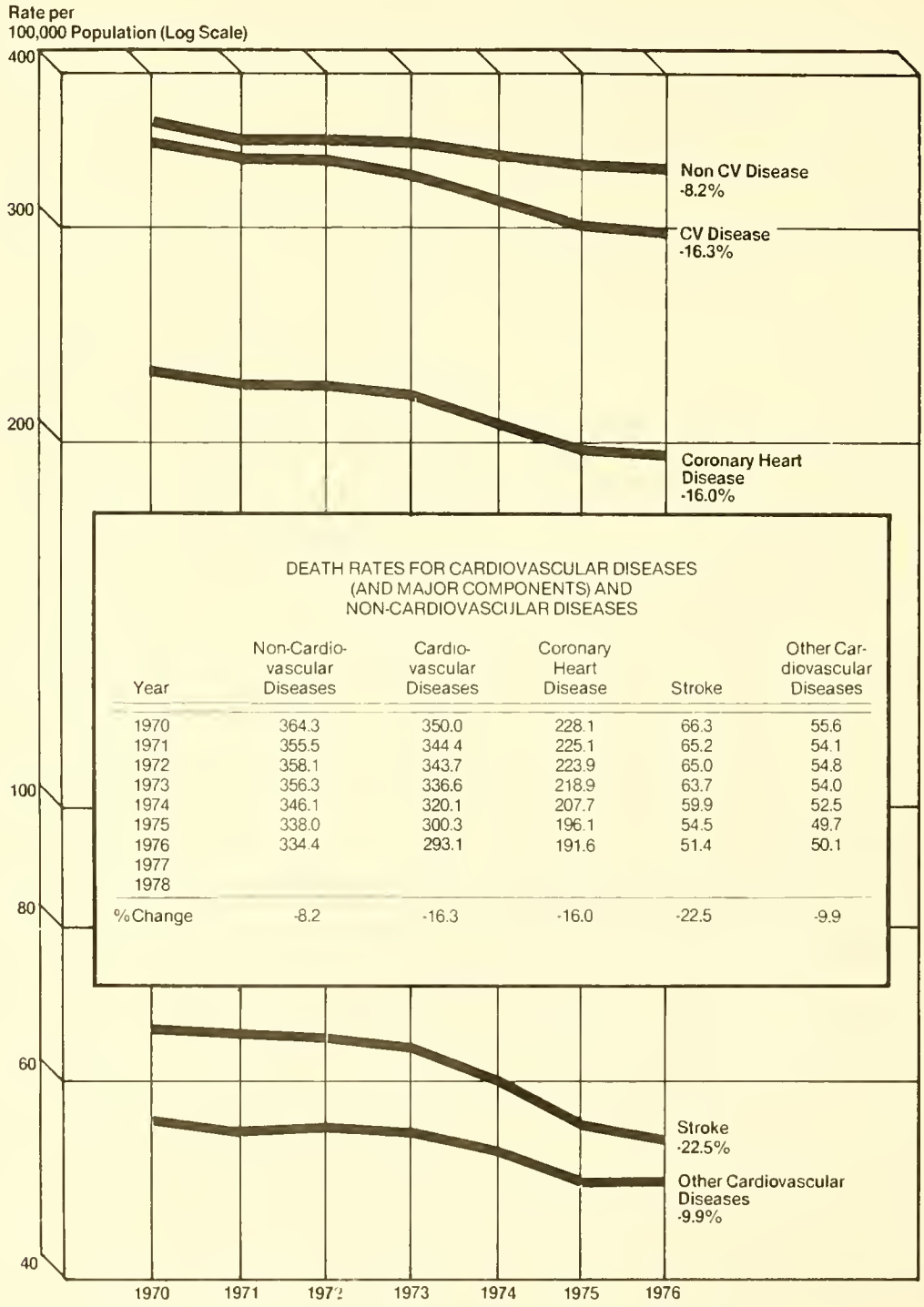
In recent years, the steady climb in death rates for cardiovascular diseases—including diseases of the heart (the major component being coronary heart disease), stroke, arteriosclerosis, and other related conditions—has been reversed (Figure 1). A decline in the crude death rate from diseases of the heart began to be noted in the period between 1950 and 1960. That trend has accelerated since 1968 (Figure 3). Age-adjusted death rates have declined 14.8 percent for cardiovascular disease and between

Figure 3: CARDIOVASCULAR* AND NONCARDIOVASCULAR MORTALITY RATES (1960-1976)**



*Excluding congenital heart disease.
**Age adjusted to U.S. population, 1940.

Figure 4: DEATH RATES FOR CARDIOVASCULAR DISEASES (AND MAJOR COMPONENTS) AND NONCARDIOVASCULAR DISEASES



DEATH RATES FOR CARDIOVASCULAR DISEASES
(AND MAJOR COMPONENTS) AND
NON-CARDIOVASCULAR DISEASES

Year	Non-Cardio-vascular Diseases	Cardio-vascular Diseases	Coronary Heart Disease	Stroke	Other Car-diovascular Diseases
1970	364.3	350.0	228.1	66.3	55.6
1971	355.5	344.4	225.1	65.2	54.1
1972	358.1	343.7	223.9	65.0	54.8
1973	356.3	336.6	218.9	63.7	54.0
1974	346.1	320.1	207.7	59.9	52.5
1975	338.0	300.3	196.1	54.5	49.7
1976	334.4	293.1	191.6	51.4	50.1
1977					
1978					
%Change	-8.2	-16.3	-16.0	-22.5	-9.9

Death rate age adjusted to U.S. population, 1940.

10 percent and 20 percent for its various components from 1970 to 1976 (Figure 4). And these declines are evident across age groups (Figure 5). In terms of deaths averted, Figure 6 shows that between 1968 and 1976, over 700,000 deaths did not occur that would have occurred had cardiovascular mortality rates remained at their 1968 levels. Deaths from major diseases of lung have also declined, but not as significantly as for cardiovascular diseases.

Clearly, declines of such magnitude indicate an overall improvement in the nation's health and the longevity of its citizens. The Bureau of the Census

Figure 5: PERCENT DECLINE IN AGE-SPECIFIC CARDIOVASCULAR MORTALITY RATES, 1968-1975

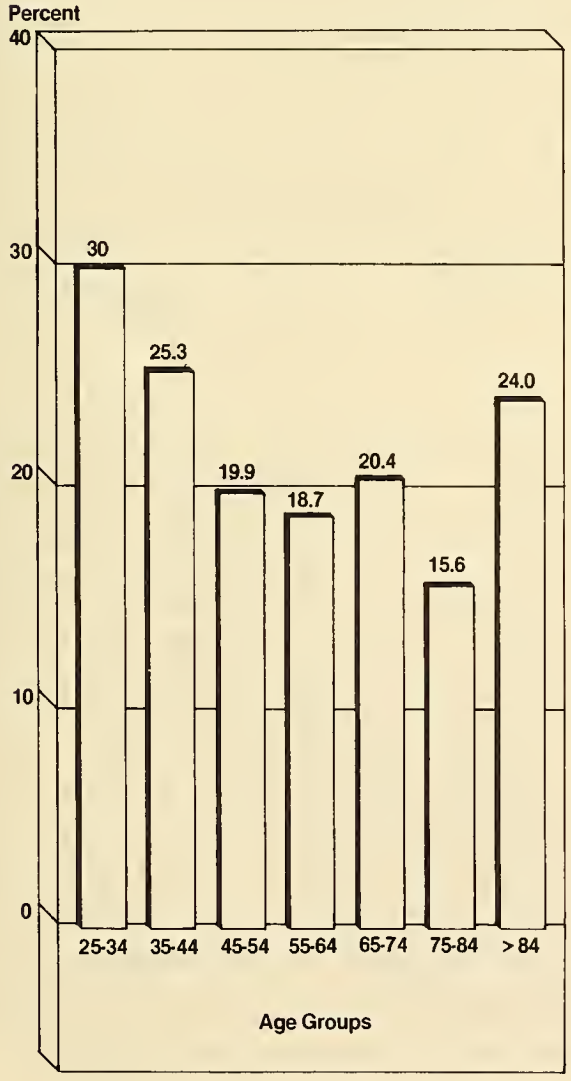


Figure 6: NUMBER OF DEATHS AVERTED DURING THE PERIOD 1969 THROUGH 1975 AS A RESULT OF THE REDUCTION OF CARDIOVASCULAR DISEASE MORTALITY FROM 1968 LEVELS, BY AGE

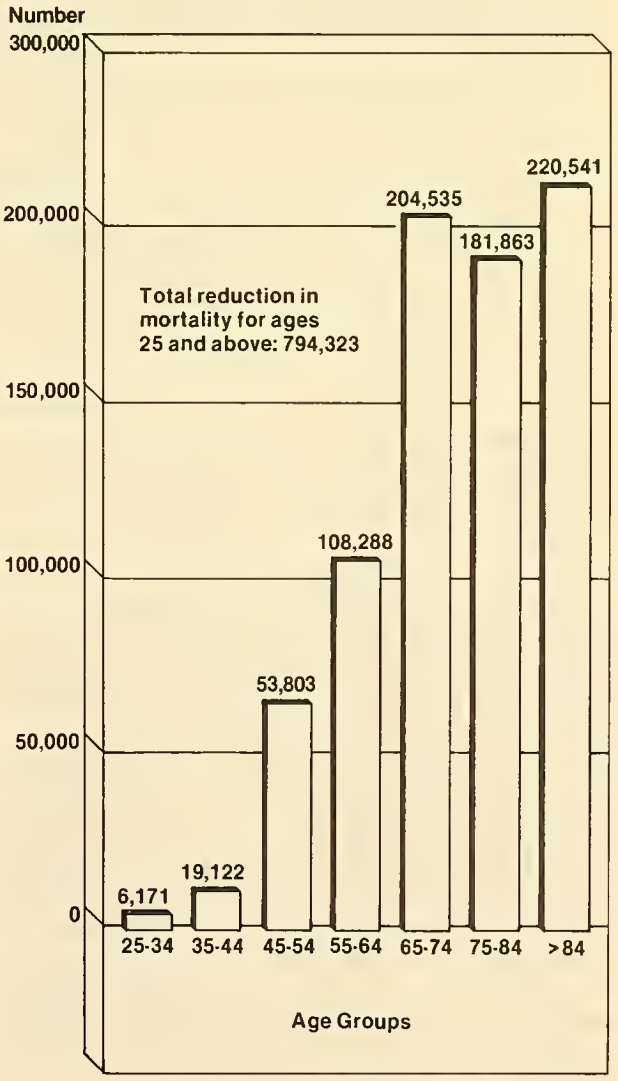
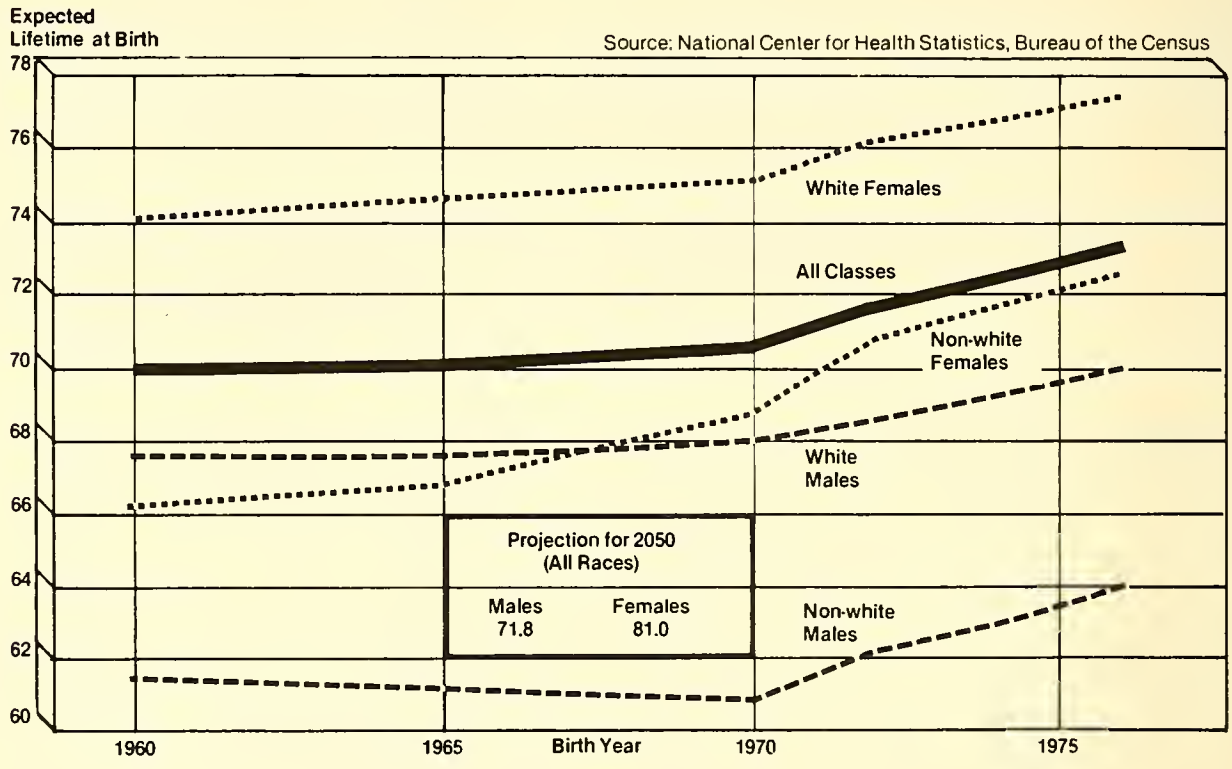


Figure 7: LIFE EXPECTANCY AT BIRTH BY BIRTH YEAR, 1960-1976



has recently reported data demonstrating a major increase in longevity due, in large part, to these declines in cardiovascular mortality (Figure 7).

IMPACT ON THE QUALITY OF LIFE

But morbidity and mortality rates and economic cost figures indicate only a part of the devastating consequences of disease. Statistics cannot communicate the effects on a young family of the early loss of a parent, the anguish of those who have suffered a crippling stroke, nor the frustration of those whose angina is so severe that climbing a few stairs is impossible. Graphs and columns of figures simply cannot reflect the qualitative consequences of disease for the individual, the family, the community, and the nation.

In the same way, statistics showing increases and decreases in morbidity and mortality rates, in disease-related economic loss, and in health care costs simply cannot convey the qualitative effects of research—its impact on the quality of life. While the ultimate goal of research is the elimination of disease-caused death, disability, and suffering through prevention, a large percentage of research continues to be directed toward discovering and developing improved means of treating existing disease so as to minimize its physical, emotional, and financial sequelae and maximize an individual's chances of enjoying a long and productive life.

Accordingly, current research efforts include: (1) programs designed to improve methods for the early diagnosis and effective treatment of the major cardiovascular, pulmonary, and blood diseases responsible for such a great deal of death and suffering, and for the rehabilitation of victims of these diseases; and (2) programs directed toward increasing our ability to recognize and deal with other diseases which, although they are less prevalent and less well known, are still potentially fatal and capable of

seriously disrupting the lives of those affected.

Following are examples of instances in which research has resulted in improvements in the quality of life that are not easily quantified through statistics.

- **Use of Echocardiography in Diagnosing Heart Problems.** Asymmetric septal hypertrophy (ASH) is an abnormality of the heart characterized by a disproportionately thickened ventricular septum. Using echocardiography, a recently developed noninvasive technique that is highly effective in diagnosing ASH, evidence has been established regarding familial prevalence and genetic transmission of this abnormality. Research conducted within the NHLBI has resulted in a significant advance in the diagnosis and establishment of inheritance patterns of ASH. The implications of these findings on the quality of life are indirect, but important. The ability to screen high-risk families and identify ASH in asymptomatic persons is a first step in determining appropriate treatment. The potential for identifying cases of ASH incorrectly diagnosed as coronary artery disease, idiopathic left ventricular hypertrophy, and "innocent" murmurs in children can also lead to more effective patient management. Accurate diagnosis of ASH by echocardiography will enable those persons predisposed to this condition to make decisions about their life style that will minimize the risk of death. In cases where thickening of the septum is determined to be life-threatening, surgical intervention may be recommended, decreasing the risk of death.

- **Treatment of Hemophilia.** Approximately 12,000 persons in the United States are known to suffer from moderate and severe hemophilia. The mainstay of hemophilia therapy consists of replacement of clotting factors derived from human plasma. Significant advances have been made in basic knowledge of the biochemistry of Factor VIII, a molecular complex consisting of procoagulant (antihemophilic) activity and platelet-related activity. Factor VIII has now been partially purified from blood. Beginning in 1964 with the development of dry concentrated Factor VIII, improvements have been made in the potency, stability, convenience, and availability of this product. The availability of Factor VIII concentrates has freed hemophiliacs from the need for whole blood or plasma transfusions, giving them the opportunity to enjoy home care along with increased freedom of activity—a major improvement in the quality of life for hemophiliacs and their families.

THE CONTINUING NEED FOR RESEARCH

Despite the encouraging progress shown by the declines in morbidity and mortality, concomitant increases in longevity, and improvements in the quality of life for many Americans, much remains to be accomplished in disease prevention and treatment. Cardiovascular disease still leads all other causes of death in the United States, with more than 640,000 persons expected to die in 1977 of coronary heart disease alone. Death and disability from chronic lung diseases appear still to be on the increase. Recent data suggest a continuous increase in death rates from chronic bronchitis and emphysema. A great deal remains to be learned about the complex hemostatic processes responsible for controlling bleeding and clotting. And although we are learning how to make life more comfortable for those afflicted with hereditary blood disorders, our ability to prevent these diseases and their crippling sequelae has not yet materialized. Similarly, we have seen considerable improvement in the management of the nation's blood resource; however, much more remains to be done before we can feel satisfied that this important resource is being optimally utilized for the benefit of all Americans.

Further progress in preventing these diseases, controlling their complications, and optimizing the use of America's blood resource will require time, effort, and resources even greater than those required to bring us to our current state of knowledge. Many years of concerted and coordinated effort still lie ahead.

As stated earlier in this chapter, the long-term goal of the NHLBI is prevention of cardiovascular, pulmonary, and blood diseases. Between 15 percent and 20 percent of the current NHLBI budget sup-

ports projects immediately related to disease prevention. That portion of the Institute's programs devoted to prevention will grow as fundamental and applied research increases our knowledge of underlying life processes and of the etiology and pathogenesis of specific diseases. Because new approaches to improved prevention will find their origin and development in the fundamental, applied, and clinical research elements of the Institute's research strategy, major emphasis will continue to be on the conduct and support of relevant, high quality investigator- and Institute-initiated research and development.

Although the Institute's primary focus is, and will continue to be, the support and conduct of biomedical research activities directed toward attainment of the long-term goal of disease prevention, its responsibility does not end with the generation and evaluation of new knowledge. Such knowledge must be translated into improved health care and health care delivery practices—effective, safe, and acceptable to consumer and provider alike—before it can have significant impact on disease prevention, diagnosis, treatment, and rehabilitation.

Thus, the Institute plans to further emphasize the importance of the ultimate applicability of the results of its research in its program planning, implementation, and evaluation efforts, and to expand those activities directed specifically toward facilitating the rapid and precise translation of research results to improving the solution of contemporary health problems. With these long-term principles as guidance, the NHLBI has reestablished for the period 1978–1982 its goals to

- conduct and support research to increase fundamental and clinical knowledge about the cardiovascular, pulmonary, and blood systems in health and disease;
- develop new and/or improved techniques for the prevention, diagnosis, and treatment of diseases affecting these systems;
- conduct and support research to increase fundamental and clinical knowledge about the nature and optimum use of the nation's blood resource;
- support the training of research scientists, clinicians, and teachers in the cardiovascular pulmonary, and blood fields;
- encourage the validation of new knowledge and the application of proven techniques by the medical and research communities; and
- fully inform both the general public and health professionals about research and clinical advances developing out of Institute programs through a comprehensive program involving information dissemination, education, and demonstration activities.

4. BIOMEDICAL RESEARCH PROGRAMS

Biomedical research is the primary means through which the NHLBI pursues its goals of preventing cardiovascular, pulmonary, and blood diseases, controlling their complications, and improving the management and utilization of the nation's blood resources. The Institute conducts and supports a spectrum of biomedical research activities—fundamental and applied research, clinical research, clinical evaluation, demonstration and education—comprising a comprehensive, coordinated, and planned program designed to achieve these goals.

The following sections describe in detail this spectrum of activities for each of the 20 program areas which make up the three major Institute foci: heart and blood vessel diseases; lung diseases; and blood diseases and blood resources. Each program area is addressed according to the following format:

- Description of the Disease Focus
- State of the Science in 1972
- Program Goals Through 1977
- Program Accomplishments Through 1977
- State of the Science in 1977
- Program Goals: 1978–1982
- Research Activities: 1978-1982
- Schedule

HEART AND BLOOD VESSEL DISEASES

In spite of the dramatic drop in cardiovascular mortality in recent years (Figures 1 and 3), over half of all deaths each year continue to be due to these diseases; they cause two-thirds of all deaths of people over 65. An estimated 30 million Americans have diseases of the heart and blood vessels, resulting in a huge burden of acute and chronic illness and disability. The economic costs are a drain on the nation; the social and psychological impacts are incalculable.

- **Arteriosclerosis** and its sequelae are the underlying causes of an estimated 87 percent of deaths from heart and vascular diseases. Virtually all adult American males and postmenopausal women are afflicted to some degree.
- **Hypertension** is one of the most commonly encountered forms of heart and blood vessel disease, affecting over 15 percent of adult Americans.
- **Coronary heart disease**, the predominant form of heart disease in the adult American, causes one and a quarter million heart attacks a year and is responsible for chronic illness in four million Americans, over half of whom are under the age of 65.
- **Cerebrovascular disease** affects 1.8 million adults of whom more than half are partially or completely disabled; 250,000 of these are between the ages of 25 and 64. Each year, nearly 200,000 persons die of stroke; another 500,000 patients are discharged from hospitals with a diagnosis of stroke.
- **Congenital heart disease** is found in about 8 out of every 1,000 infants born each year;

over half of the 6,500 deaths each year occur in infancy.

- **Acute rheumatic fever and subsequent rheumatic heart disease** occur in school age children at a rate of about 2-3 per 1,000; an equal number have rheumatic fever without heart disease. More than 13,000 deaths occur a year from this disease and its cardiac complications.

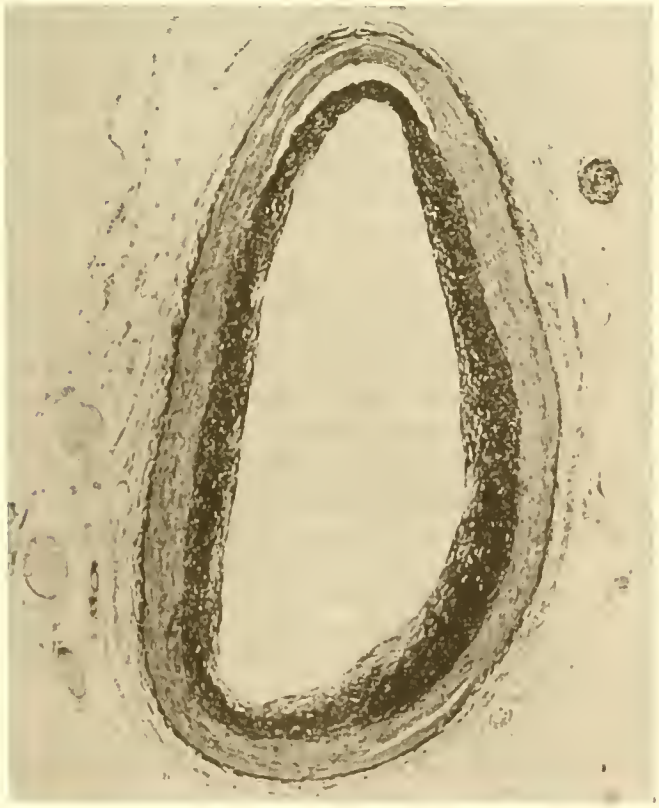
The evidence of progress in the prevention and treatment of these diseases is most heartening. But the loss of life, disability, and economic, social, and individual burdens which they continue to cause are still unacceptable. Our best hope for further progress in the prevention and treatment of these diseases and their consequences still rests with research. NHLBI research programs directed toward fulfilling that hope are described in the following pages.

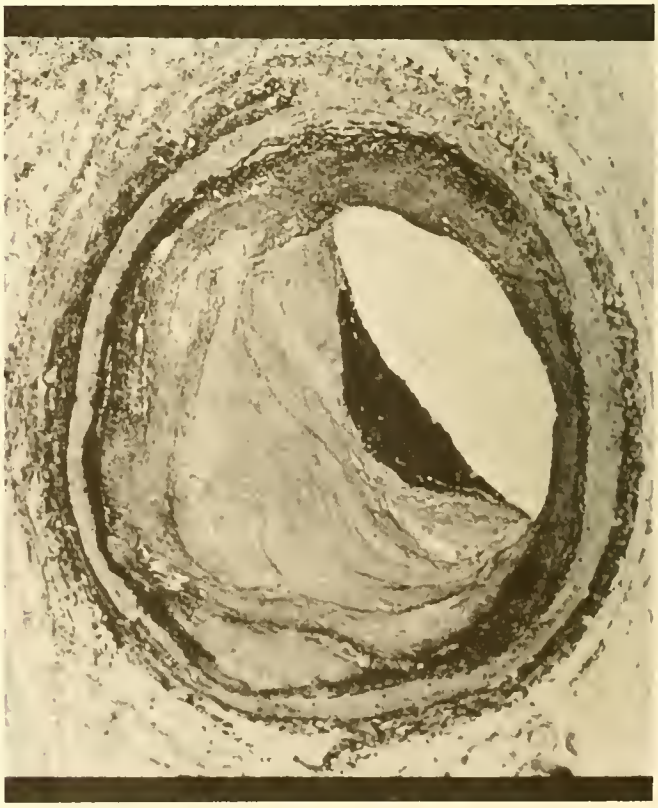
Arteriosclerosis

Arteriosclerosis, or hardening of the arteries, is a chronic disease characterized by progressive pathological changes in the blood vessels that nourish the organs of the body. Its most common form is atherosclerosis, in which the inner lining of the arteries becomes rough, thick, hard, and covered with fatty deposits called atheromatous plaques. Eventually the inner diameter of the vessels decreases, and blood flow diminishes or stops. When this happens, the condition can manifest itself as heart attack, sudden death, angina pectoris, stroke, or occlusive disease of a peripheral vessel. Atherosclerosis begins early in life and is asymptomatic for years. Virtually all American adults, especially men and postmenopausal women, are afflicted to some degree.

State of the Science in 1972

In 1972, more than one million deaths in America were due to heart and blood vessel diseases. Of these, 87 percent were attributable to arteriosclerosis and its sequelae. At that time, as now, the causes of arteriosclerosis were not well understood, nor were means of preventing or re-

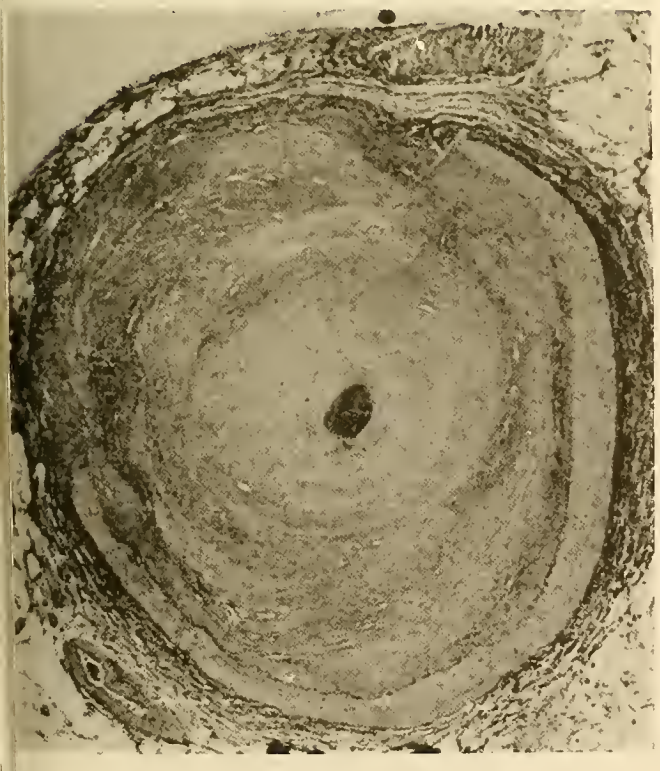




versing the disease known. However, several important clues had been discovered from epidemiologic studies of populations. On the basis of statistical associations, three major risk factors were identified—elevated blood cholesterol levels, high blood pressure, and cigarette smoking. A number of additional risk factors were also recognized—diabetes, physical inactivity, obesity, age, male sex, and certain personality types.

There was a growing awareness at that time that arteriosclerosis was not a disease confined to older people or to men only, but that women and young people were also at risk. The concept that arteriosclerosis could begin during childhood and continue to develop slowly but surely throughout adulthood was beginning to receive attention.

With the major risk factors for arteriosclerosis pinpointed, the way was open for programs that would attempt to modify these factors in the population. In fact, as early as 1962, a group supported by the National Heart Institute had advocated the undertaking of a large-scale, long-term prospective study to test the hypothesis that coronary heart disease could be prevented by dietary measures in an open population. However, in 1971, a Task Force on Arteriosclerosis felt it unwise to mount a single, major, national diet-heart trial in the general population, expressing skepticism that a meaningful answer could be obtained or that the study could be carried through to completion.



Instead, the Task Force recommended a more cautious approach, the sponsorship of limited clinical trials in three areas: first, a program in target populations to test the "risk factor" hypothesis, to see whether in fact controlling these factors would decrease the morbidity and mortality from the complications of arteriosclerosis; second, continuation of the Coronary Drug Project begun in 1969, to test the usefulness of certain drugs in lowering lipids in the blood; and third, expansion of the Lipid Research Clinics program, first implemented in 1971 and designed to collect information on patients with different types of hyperlipoproteinemia (high levels of lipids carried in the blood).

In addition to these developments, a number of research findings at that time pointed to possible genetic influences on the metabolism of lipoproteins, on the excretion of sterols, and on the atherogenic reaction of the arterial wall. Furthermore, with progress in cellular and biochemical research, particularly in certain enzyme studies and in collagen and mucopolysaccharide chemistry, the techniques were at hand for better understanding the metabolism of the artery wall and its role in plaque formation.

In 1972, there was an inability to diagnose arteriosclerosis effectively and, clinically, no therapy existed to control or reverse plaque development. However, the availability of such techniques as ultrasound, x-ray densitometry, and computer-assisted image enhancement of complex image signals set the stage for the development of better diagnostic procedures.

Cross-sections of the arteries from three patients illustrate the atherosclerotic process. On the left is a normal healthy artery. The middle artery has a considerable accumulation of fatty deposits and is already significantly blocked or occluded. The artery on the right illustrates the narrowing of the lumen to such a degree that the blood flow is serverely restricted.

With the convergence of all of these leads, the opportunity for initiating a number of different programs presented itself to the Institute. In 1971, the Task Force on Arteriosclerosis assessed research needs and made recommendations of priorities for future Institute programs in this area. The report of the Task Force formed the basis of the Institute's goals for the next five-year period.

Goals Through 1977

In 1972, the Institute established the following broad goals to guide its research program on arteriosclerosis:

- Develop a better understanding of the basic mechanisms, processes, and sequelae of arteriosclerosis.
- Develop improved methods for the diagnosis and treatment of arteriosclerosis.
- Encourage psychologists, sociologists, and behavioral scientists to study the problems associated with rehabilitation of patients with arteriosclerosis.
- Define those circumstances that may promote the prevention of arteriosclerosis.
- Establish colonies of animals, especially nonhuman primates suitable as models for use in arteriosclerosis research.

The Institute planned to achieve these broad goals by combining the expertise and resources available in traditional research laboratories, with those available through recently initiated multidisciplinary programs such as the Specialized Centers of Research on Arteriosclerosis and clinical trial programs like the Lipid Research Clinics program, the Coronary Drug Project, and the Multiple Risk Factor Intervention Trial.

Accomplishments Through 1977

There have been many accomplishments since 1972. Some of these have been so significant as to give new direction to future studies and hope for noteworthy progress in diagnosis, prevention, and treatment of arteriosclerosis.

- The past five years have seen a large gain in knowledge about the **structure and function of lipoproteins**—large molecules in the blood which transport fats and cholesterol. Whereas low density lipoproteins have been known to be associated with an increased risk of coronary heart disease, recent cross-sectional and prospective studies indicate that high levels of high density lipoproteins (HDL) in blood lower the risk of developing coronary heart disease. This suggests that there may be natural mechanisms that protect against the development of atherosclerosis. The level of HDL is inversely, strongly, and independently correlated with the risk of developing coronary heart disease. Biochemical investigations suggest that HDL may be involved in removing cholesterol from the arterial wall or in preventing its deposition there.
- Preliminary results from the Lipid Research Clinics' (LRC) population studies and from the Multiple Risk Factor Intervention Trial (MRFIT) indicate **dietary change in the American population.** Intake of cholesterol and saturated fats has decreased. For the first time, an inverse relationship has been found between education and/or socioeconomic status and levels of blood lipids. Significantly lower levels of blood lipids and lipoproteins have been observed in subjects in higher educational and economic categories. These findings are compatible with improved awareness within certain population groups of coronary risk factors and their prevention.
- **Nutrition studies** have been coordinated with those of other governmental and nongovernmental agencies. Information has been updated and disseminated on the **composition of foods** relevant to heart and vascular disease. The NHLBI Table of Food Composition, recently made available to the scientific community, was developed with particular emphasis on fats and cholesterol. Recognizing that current food composition data are inadequate, the Institute is funding a review of the literature by the United States Department of Agriculture and collection of data on the lipid content of food. Data on fatty acids have been summarized for milk and

dairy products, eggs and egg products, beef, fin fish, and cereal grains. A revised "Exchange List for Meal Planning" has been prepared based on new information on food composition and on improved methods of patient counseling. The revision also promotes the use of the fat-control aspects of diet for treatment of diabetes and obesity and other diseases for which quantitative and qualitative diets are advised.

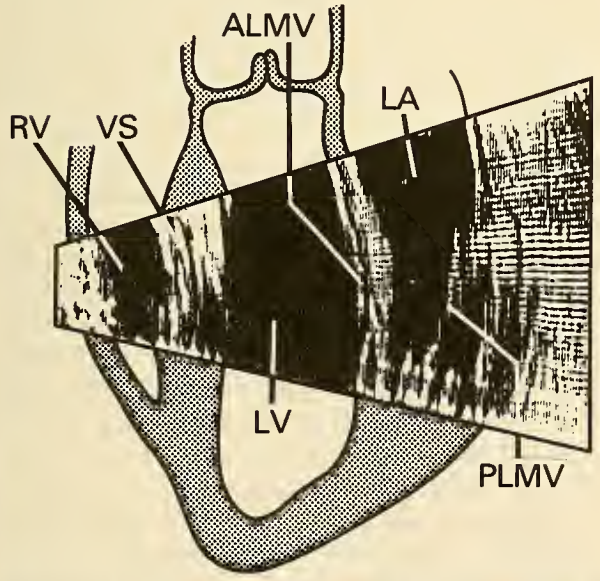
- Information about **risk factors** is now becoming more specific and provides important indications for future studies and planning of education programs. Knowledge about risk factors is important for early identification of people likely to be susceptible to arteriosclerosis.
  - *Several causal mechanisms relating cigarette smoking to coronary heart disease* have been confirmed by research both in animals and humans. The release of catecholamines, increased platelet adhesiveness leading to clotting, formation of carboxyhemoglobin, and creation of an imbalance between myocardial oxygen supply and demand have all been demonstrated in smokers and are possible explanations for the excess coronary heart disease mortality and morbidity among smokers.
  - People can definitely be persuaded to stop *smoking*. In general, more middle-aged men have stopped smoking than have individuals in other groups. Two-thirds of smokers are able to stop smoking, and one-third never take up the habit again. Long-term prospective studies have indicated that those who give up smoking tend to return to normal risk factor levels over time. Persons who have stopped smoking have been shown to have a reduced incidence of coronary heart disease.
  - The MRFIT programs have concentrated on combined *risk factor intervention* in high-risk patients. The intervention program is designed to achieve and maintain a lowering of elevated serum cholesterol, a reduction in elevated blood pressure, and cessation of cigarette smoking. The results from cigarette smoking intervention appear to be more successful than those in previous smoking cessation programs. Reduction of serum cholesterol through dietary changes has proved more difficult to achieve.
  - As data describing populations of children become available, the Institute synthesizes the data on *risk factors in children*. Natural history data are prerequisites for distinguishing normal from abnormal conditions, and for conducting in-depth etiologic and prevention studies. Four Specialized Centers of Research (SCORs) have collected blood pressure and lipid data on 10,000 children 2–18 years old. The data have been analyzed and are being integrated into a monograph suitable for wide distribution. Charts for use in primary care practices have been developed for blood pressure determination in children. These charts are similar to the height-weight charts in widespread use and are normative for age and sex.
- **Plasma cholesterol and triglyceride distributions** have been established for a group of diverse, geographically dispersed populations. These are likely to become standard reference data for the American population in the future.
- Recently, **new upper limits for the clinical diagnosis of hypertriglyceridemia** have been designated, placing more people within "normal" ranges, although they may still be at risk. These new limits will considerably decrease the number of subjects diagnosed as having Type IV hyperlipoproteinemia.
- The impact of **oral contraceptives** on blood lipids has been evaluated more completely on a population scale. It has been confirmed that oral contraceptives elevate cholesterol and triglyceride levels, especially the latter, and account for about 50 percent of the hyperlipidemia observed in younger women.
- The results of clinical experiments to reduce

elevated levels of **blood cholesterol** through the Coronary Drug Project were announced in 1975. The study had evaluated the possible efficacy of several drugs with the potential to lower lipids in patients who had had at least one heart attack. Three drugs were dropped from the study because their adverse effects outweighed their benefits. The two drugs that were continued for the entire duration of the study, clofibrate and nicotinic acid, had no effect on mortality. Furthermore, clofibrate was associated with a high degree of cardiovascular morbidity, and nicotinic acid (although it decreased angina and new heart attacks) was associated with a high incidence of undesirable side effects. This lack of effectiveness makes the use of these drugs in post-myocardial infarction patients unjustified. These important results have been widely circulated in the medical literature.

- **Genetic** studies of newborn infants have revealed a definite mode of inheritance for Type II hyperlipoproteinemia, determined by a single gene. A companion analysis of over 1,000 relatives of affected patients conducted within the NHLBI is the most extensive study of this genetic defect ever undertaken. This project provides striking evidence of the premature risk of patients affected with this disorder. An understanding of the possible mechanisms of familial hypercholesterolemia has been furthered by the finding that cells from the skin (fibroblasts) of affected individuals differ from those of normal individuals in their limited ability to bind and degrade a specific serum lipoprotein, low density lipoprotein (LDL), which is found in abnormally high concentrations in these hypercholesterolemic individuals. The NHLBI Twin Study has demonstrated a significant genetic contribution to the variability of height, weight, blood pressure, vital capacity, glucose intolerance, uric acid, and plasma triglycerides, but the data on genetic determination of cholesterol and lipoproteins are ambiguous. To clarify this question, plans are being made to study adult dichorionic and monochorionic identical twins.
- **Insulin-dependent diabetes** is a major factor for cardiovascular disease in both men and women. The Framingham Study provided the major prospective data indicating that diabetes is significantly and independently associated with coronary heart disease, stroke, and peripheral vascular disease. These observations led the Institute in 1976 to stimulate research in diabetes and cardiovascular disease. As a result, additional investigators across the country are currently studying basic mechanisms of diabetes as they apply to the cardiovascular component of this disease.
- **Pathogenic studies** have added new insights into how atherosclerosis might develop. Among the theories currently under investigation and attracting considerable attention is the **injury-repair hypothesis.** Plaque development may start with any kind of injury to the inner lining (endothelium) of the arteries. The injury may be caused by mechanical denuding of the inner lining of the artery (for example, by the intra-arterial shearing and flow effects caused by high blood pressure) in combination with elevated blood lipids, or other unknown agents. The injury-repair hypothesis, linking many earlier unrelated observations, proposes that the initiation and subsequent enlargement of atherosclerotic lesions require sequential and interrelated cyclic events. The first cycle may produce eventual healing after a single injury to the endothelium. The second occurs if the initial attempt at healing is followed by further injury. Such injury leads to repeated formation of multiple layers of smooth muscle cells and the accumulation of intracellular and extracellular lipids (fats) and connective tissue, thereby increasing the size of the lesion and causing it to protrude into the inner lumen of the artery. This protruding portion of the arterial wall is more susceptible to future injury, thus causing the injury cycle to repeat itself. During enlargement, thrombosis may occur, and calcium may also be deposited into the lesions, resulting in a still more complex, calcified atheroma. Recent experiments indi-

cate the **blood platelet factors** promote smooth muscle cell proliferation after vessel injury. This is being studied with the potential goal of developing anti-platelet factor drugs which could prevent plaque formation.

- The nature of the protein moieties that solubilize lipid in the blood—the apoproteins—has been extensively characterized. Seven different apoproteins have now been described. Five of these have been completely sequenced; three have been resynthesized, allowing their metabolism as well as the nature of their lipid binding to be more clearly defined. The catalytic action of two of these apoproteins in intravascular lipolysis and cholesterol esterification has been described. Clinical reports are now appearing about lipoprotein transport abnormalities secondary to alterations in one or more apoproteins. Immunoassay techniques capable of readily quantifying the levels of these apoproteins in health and disease have recently become available.
- **Plaque development can be reversed in nonhuman primates** and other animals made atherosclerotic by a high-cholesterol diet. Both dietary and drug intervention lowered serum cholesterol levels. Plaques in rhesus monkeys with severe atherosclerosis were reversed by a low-fat diet. These data gained from animal studies will be important in guiding scientists in future research on the regression of plaques in human populations. Lipoprotein metabolism and response to dietary cholesterol have been found to correlate with genetic variations in several species of animals. Breeding colonies of nonhuman primates are being developed to provide a resource of animals modeled for arteriosclerosis and hypertension.
- A number of promising approaches to **better diagnostic procedures** and techniques are being developed, including videometry and videodensitometry, ultrasound, radionuclear angiography, and improvements in traditional coronary angiography. The use of computer-



Ultrasound is a noninvasive technique for visualizing internal organs of the body. Two of the many uses of this technique are illustrated above. On the left, a narrow cross-section of the heart is visualized in an echocardiogram. This process allows the viewer to examine tissue layers in their true perspective relationships, one to another, rather than on a single plane as in an x-ray film. The photo on the right shows a transmitter and receiver being held against the neck of a patient. A picture of the interior of the carotid artery can be seen on the screen. The presence of arteriosclerotic placque can be determined by this method.

controlled image enhancement and measurement is proving valuable in measuring the progression or regression of femoral atheroma. These techniques have already been used in man, but they need further refinement, particularly in the area of lesion progression and regression.

- **Community-based field trials** have been initiated to collect data relating risk factors to cardiovascular disease. This is a prelude to translation of the results of clinical trials into effective methods of reducing the risk of cardiovascular disease. Important baseline data are being collected over a number of years on community activity with respect to such risk factors as nutrition, smoking, hypertension, and the incidence and prevalence of cardiovascular disease within communities. Such an information base is required to relate changes over time to activities within the community, and to identify people most susceptible to arteriosclerosis.
- As a mechanism for integrating programs in research, demonstration, prevention, control, education, and clinical application, the Institute established a **National Research and Demonstration Center** in cardiovascular disease in 1975. The Center is devoted primarily to arteriosclerotic disease. The experience so far suggests that the combination of research and community outreach programs in the same environment enhances the translation of research findings into health care application. The Center encourages, facilitates, and coordinates interactions between scientists (including social and behavioral scientists) and practitioners of various specialties.

State of the Science in 1977

In 1975, the number of deaths from major cardiovascular diseases dropped below one million, the first such instance since 1964. While the reasons for this trend are complex and varied, there is little doubt that the giant effort to learn more about arteriosclerosis is beginning to yield answers and results.

In 1972, the major risk factors associated with arteriosclerosis were known, but it was not clear that the public could be persuaded to alter its habits in order to decrease the risk of developing cardiovascular diseases. As the result of expansion of risk factor identification and reduction activities such as the Lipid Research Clinics program and the Multiple Risk Factor Intervention Trial, we can now say with confidence that dietary and smoking interventions are possible and may be beneficial. Per capita consumption of butter, eggs, whole milk, and fats of animal origin has fallen, while ingestion of vegetable fats and oils has increased. Cholesterol levels in the blood of Americans appear to have dropped an estimated 5 to 10 percent from levels determined two decades ago. Contrary to previous reports, initial analysis of data from the Lipid Research Clinics program shows that both men and women employed in the higher occupations and with higher educational attainment now tend to have lower cholesterol levels and substantially lower triglyceride levels than do individuals in lower socioeconomic categories.

Although large numbers of young men and women are apparently taking up the smoking habit, others, particularly middle-aged male smokers, are stopping. Between 1964 and 1975 the proportion of male smokers decreased in all age groups. Persons who stop smoking have been shown to have a reduced incidence of coronary heart disease compared to persons who continue to smoke.

The recent finding that high levels of high density lipoprotein in the blood can lower the risk of developing coronary heart disease is an important new development, suggesting that some individuals may be protected naturally against atherosclerosis. Apparently high density lipoprotein is active in either removing cholesterol or preventing it from accumulating in the arterial wall. This information may lead to new types of therapy.

Genetic studies on individuals with Type II hyperlipoproteinemia have indicated that affected individuals differ from normal individuals in their limited ability to bind and degrade low density lipoprotein, thus accounting for the high plasma cholesterol levels.

A major new and fundamental concept in atherogenesis is the hypothesis that a single smooth muscle cell lining the wall of an artery may undergo

cellular mutation and become transformed. The result is cell proliferation and the development of a growth or plaque that protrudes into the lumen of the artery, leading to the clogging, diminished blood flow, or complete stoppage characteristic of arteriosclerosis. The significance of this hypothesis is that, if true, it means that mature atherosclerotic plaques are monoclonal; that is, all cells within the plaque have arisen from a single mutated cell and thus are uniform with respect to biochemical and cellular features. Aside from its importance as an explanation for the origin of atherosclerotic plaques, this theory may lead to more effective therapy. If all cells in a plaque are in fact derived from a common parent cell, then one would expect all cells in the plaque to respond uniformly to therapy. There are also new insights into how atherogenesis might be triggered. When blood platelets bump against the inner wall of a blood vessel, the platelets are stimulated to release prostaglandin endoperoxides that, in turn, are converted to thromboxane, a promoter of platelet aggregation. The hypothesis is that an intact vessel lining releases an enzyme which enables the endoperoxide to be converted to prostacyclin (an inhibitor of platelet aggregation) instead of thromboxane. A damaged vessel lining apparently does not release this enzyme. It is further hypothesized that these reactions are normally in balance so that the accumulation of platelets and their stimulation of vascular smooth muscle cells to proliferate and form plaques do not occur. Thus, in this scheme, an imbalance between the local production of thromboxane and prostacyclin may be an important basis for plaque formation.

The growing recognition that arteriosclerosis and other heart diseases may have their origin in childhood has led to the recent formation of a Task Force on Heart Disease in Childhood. The Task Force is charged with recommending to the Institute what research areas are important for greater understanding of the etiology, prevention, and control of heart disease in both children and adults.

As the roles of known risk factors become clearer, it is becoming apparent that there are atherosclerotic complications not explained by those factors. Current knowledge of major risk factors explains some of the variances, perhaps as much as 70 percent, but many individuals who have heart attacks are not at risk in conventional terms. Other risk factors have been suggested based on preliminary evidence—for example, trace metals in the water supply, emotional stress, and arterial inflammation from unidentified causes—but little is known about them. Clearly, future research is required.

There is considerable reason for encouragement as we move closer to our goal of prevention and control of arteriosclerosis. Emphasis on heart disease in children and the possible relationship of childhood patterns and characteristics to the later appearance of heart disease in adulthood are promising new developments. The stimulation of more investigations on diabetes and cardiovascular disease should yield important new information. And last, but not least, the complex task of convincing the American people to change their life styles and such habits as smoking and eating will go forward with an increasing awareness of economic, psychological, emotional, and cultural considerations.

Program Goals: 1978–1982

The Institute's mission is to improve the diagnosis, treatment, cure, and prevention of arteriosclerosis and arteriosclerotic disease beyond that which is possible at present. The following goals have been developed to serve as guidelines for research activities during the next five years:

- Gain a better understanding of the pathogenetic mechanisms in arteriosclerosis.
- Further specify associated or causal disturbances and associated risk factors for arteriosclerosis.
- Define those circumstances that may promote the regression and/or prevention of arteriosclerosis.
- Develop information on behaviors that promote or inhibit the application of knowledge about arteriosclerosis to its prevention, diagnosis, and/or treatment.

Research Activities: 1978–1982

The chief priority of the Institute's research activities continues to be the achievement of a better understanding of atherogenesis and the application

of this information to more effective diagnosis, treatment, and prevention of arteriosclerosis. It has become increasingly clear that while we can predict susceptibility to atherosclerosis by analysis of an individual's risk factors, many cases of disease remain unexplained and additional causal and risk factor data must be found. To this end, the Institute will continue basic and applied research and initiate a number of new studies.

Continuing research efforts include:

- Studies on the cellular mechanisms of atherogenesis.
- Increased involvement of investigators from the fields of blood coagulation, blood platelet research, and thrombosis in order to elucidate the effects of platelets and normal and abnormal plasma constituents on atherogenesis.
- Pathogenetic studies including those designed to elucidate the nature and significance of arteriosclerosis or its risk factor antecedents in childhood.
- Further development of our understanding of the roles of diet and nutrition in atherosclerosis and its control.
- Development and implementation of the bioassay for cardiovascular disease of less hazardous cigarettes (in collaboration with the Smoking and Health Program of the National Cancer Institute) and determination of why smoking promotes atherosclerosis.
- Research on diabetes mellitus as a risk factor for, and important participant in, many aspects and mechanisms of cardiovascular disease.
- Multigenerational, longitudinal, and epidemiological studies in Framingham and other cohorts.

Studies to be implemented:

- Research on the role of local and humoral substances — prostacyclin, prostaglandins, thromboxane, and other prostaglandin stimulators and inhibitors—on vessel reactivity, smooth muscle cell proliferation, and the atherosclerotic process.
- Research on the genetics of hyperlipidemia and on other risk factors and their potential role in coronary heart disease prevention.
- Research on the possible monoclonal origin of arteriosclerosis and on the role of intimal smooth muscle cells and platelets in atherogenesis.
- Utilization of the non-human primates resources developed for research in arteriosclerosis, cerebrovascular disease, and hypertension.

Studies under consideration for increased support:

- Research on the identification and study of additional "risk factors," with the objective of elucidating additional causes of premature coronary heart disease and other atherosclerotic complications. This effort will include basic, clinical, and epidemiologic research and will encourage studies of animal models, infants, and children. Special attention will be given to identifying risk factor antecedents of arteriosclerosis in childhood.

Schedule

The clinical trials described will have completed their compilation of information within the next five-year period. Specifically, for example, the MRFIT is planned to complete participant follow-up in FY 81, with continuing support needed for data analysis through FY 83.

A joint study with the National Institute of Arthritis, Metabolism, and Digestive Diseases, now under active consideration, deals with a clinical trial to evaluate the effectiveness of tight control of juvenile diabetes. This study might begin in pilot form in 1978 and continue through 1982.

Studies designed to elucidate the nature and significance of arteriosclerosis or its risk factor antecedents in childhood are planned to begin in 1978 and continue through 1982.

Information and hypotheses identified at a workshop on "The Regression of Arteriosclerosis in Man and Animals" will provide the basis for increased activity in this area to begin in 1979 and continue through 1982.

A major increase in research emphasis on the cellular mechanisms of atherogenesis is planned for 1978–1980. As a result, it is hoped that the cellular biology research community will be an integral part of research in this area by 1981.

A research activity to elucidate the effects on platelet function of normal and abnormal plasma constituents thought to influence atherogenesis is planned to start in FY 79 and continue into FY 80.

A special effort to promote the enhanced use of non-human primates for research in atherosclerosis is planned to start in FY 78 and continue through FY 82.

Hypertension

Hypertension, or high blood pressure, is a leading cause of disease and death in the United States. It can occur in both sexes, in all races and nationalities, and in all economic groups. However, variations in susceptibility within groups have been recognized; for example, the incidence is higher in males over 50, and higher in blacks than in whites.

At least 90 percent of Americans who are hypertensive have essential hypertension—elevated blood pressures for unknown reasons. The remaining cases are related directly to specific identifiable abnormalities.

Hypertension is easy to detect, but the condition is frequently unsuspected since it is asymptomatic in most instances. Blood pressure readings have two components: systolic and diastolic. The systolic or "upper" blood pressure reading is a measure of the pressure in the arteries exerted by the heart when the left ventricle contracts, forcing blood from the heart into the aorta. The diastolic or "lower" blood pressure reading measures the blood pressure present during relaxation of the heart.

Mild hypertension is defined as diastolic pressures between 90 and 94 mm Hg; moderate hypertension as systolic pressures in excess of 160 and diastolic in excess of 94 mm Hg; and severe hypertension as systolic pressures in excess of 180 and diastolic in excess of 115 mm Hg. Blood pressures in both moderate and severe ranges are associated with increased morbidity and mortality and constitute a major risk factor in the development of stroke, heart failure, and kidney disease. Mild hypertension is also associated with an increase in morbidity and mortality.

State of the Science in 1972

By 1972, drug therapy for controlling hypertension in severe and moderately severe cases was available and effective. It had already been shown that the risks of stroke, heart failure, and kidney failure could be significantly reduced in patients who received adequate antihypertensive drug therapy. The therapy, however, involved lifelong adherence to a drug regimen which often had unpleasant side effects. It was thus clear to the scientific community in 1972, as now, that a matter of high priority would be to find the cause or causes of hypertension in order to prevent its development. At that time, the etiology of hypertension was not known nor was its pathophysiology clear, although many leads were available.

Hypertension was thought to be a condition resulting from a breakdown in the complex control system that maintains equilibrium between blood flow and the constricting and dilating forces of the arterial walls. The regulation of normal blood pressure was pictured as dependent upon a balance of hemodynamics, humoral, and many other factors operating at one time.

It had been known for 150 years that the kidney was implicated in hypertension. There was considerable evidence by 1972 to indicate that the kidney had a blood pressure elevating function and possibly a blood pressure lowering function. Renin and angiotensin were two substances linked to the elevation of blood pressure.

The adrenal cortex was also believed to have some relationship to hypertension since drugs which antagonized the action of the mineralocorticoid hormone aldosterone had proved useful in the treatment of some forms of hypertension. Similarly, the autonomic nervous system was suspected of being important, since manipulation of this system with blocking agents and drugs had proved effective in lowering elevated blood pressure. Salt intake was also believed to play a role in the genesis of hypertension, but the nature of the relationship needed further clarification.

Hypertension is widespread in the black population. Early detection is essential to prevent the serious complications of hypertension such as kidney disease and stroke.

Prior to 1972, a suitable animal model of human essential hypertension was not widely available. This limited research on the etiology and pathophysiology of hypertension, especially the biochemical and genetic aspects of the problem. Clinical trials and demonstration programs were also needed to determine the benefits of drug therapy. Recognizing that a balanced research effort, including all aspects of the problem, was required, the Institute moved forward to intensify its hypertension research program.

Goals Through 1977

Two broad goals, one short-range and the other long-range, were set by the Institute in 1972 as a guide to its research efforts:*

- Short-range goal: to optimize the utilization of currently effective treatment for hypertension.
- Long-range goal: to prevent hypertension.

The actions taken to implement these goals can be grouped into four major categories: studies related to the etiology of hypertension; clinical trials to investigate the effects of therapeutic intervention; epidemiologic studies; and the development of animal models with spontaneous hypertension.

Accomplishments Through 1977

Etiology. Much new information is now available on the possible roles of such substances as renin, angiotensin, mineralocorticoids like aldosterone, kallikrein, and prostaglandins in the etiology of hypertension. Some of the accomplishments in this area are:

- Studies on **renin-dependent forms of human hypertension** suggest that most or all forms of essential hypertension exhibit a renin factor contributing to the elevation of blood pressure. Studies using angiotensin antagonists or the angiotensin I converting enzyme inhibitor suggest that a critical relationship appears to exist between renin, angiotensin, and sodium balance. While the role of renin as an initiating factor in essential hypertension is not clear, the therapeutic implications of renin-dependent hypertension are becoming more apparent.
- Basic and clinical investigations on **the role of mineralocorticoids** like aldosterone in hypertension continue to receive emphasis. Studies are attempting to understand the meaning of elevated plasma concentrations seen in some patients with essential hypertension. The role of mineralocorticoids in human hypertension may be more significant than was originally believed.
- One biochemical alteration has now been correlated with elevated blood pressure. **Urinary kallikrein excretion,** which is lower in adults with essential hypertension, has recently been studied in children. Urinary kallikrein concentrations were found to be significantly lower in black normotensive children than in white normotensive children. Families with the lowest mean kallikrein concentrations tended to have higher blood pressures than those with the highest kallikrein levels. While this study does not clearly implicate urinary kallikrein in the pathogenesis of essential hypertension, it nevertheless suggests a potential relationship between this biochemical marker and blood pressure.
- The observation that a **defect in renal prostaglandin metabolism** may contribute to the development of hypertension in rats genetically prone to hypertension has been confirmed. This suggests that a biochemical defect could be the inherited abnormality responsible for the development of hypertension in this animal model.
- Newly developed or greatly improved **assays for the measurement of angiotensin, aldosterone and other mineralocorticoids, prostaglandins, renin, and kallikrein** have been perfected in specialized laboratories to help clarify the role of these factors in the etiology of hypertension.

*See also the chapter on prevention, education, and control.

Clinical Trials. Several clinical trials are in progress, the main goal being to evaluate the effectiveness of intensive antihypertensive therapy.

- **The Hypertension Detection and Follow-up Program (HDFP)**, a cooperative clinical trial, is now in its third year with 95 percent of the third year follow-up completed. The trial is attempting to determine the effectiveness of intensive antihypertensive therapy in reducing mortality and morbidity from hypertension in general community populations. An important component of the HDFP involves behavioral research as it relates to the identification of factors that enhance adherence to therapy and to the assessment of personal attitudes toward hypertension. The subject pool for the HDFP consists of 10,940 hypertensive patients from 14 communities. Cross sections of racial and ethnic groups and different socioeconomic strata in rural, urban, and suburban communities are being studied. Findings indicate that 79 percent of the participants who were maintained on a "stepped-care" approach are still active in the program. **The concept of stepped-care approach to treatment** calls for initiating therapy with a small dose of an antihypertensive drug, increasing the dose of that drug, and then adding, one after another, other drugs as needed. The dose of each drug initially is low and subsequently is increased as needed to reach a predetermined therapeutic goal. The plan should include periodic reevaluation of blood pressure and regimen adjustment up or down as needed. Stepping down the drug dose, whenever possible, without compromising control, is obviously desirable. While the third year data are still incomplete, two-thirds of the stepped-care patients had diastolic blood pressures in the normal range after two years of follow-up. The average decline in diastolic blood pressure over the first two years of treatment was a substantial 14.4 mm Hg.
- Hypertension is one of the major risk factors for heart attacks currently being studied in the **Multiple Risk Factor Intervention Trial** (MRFIT). Data from this study will help to determine whether a significant reduction in heart attacks can be achieved by the reduction of the combined risk factors of high blood pressure, high blood cholesterol, and cigarette smoking in men at risk of coronary heart disease.
- Among its other efforts toward improving hypertension therapy, NHLBI has recently completed collaborative studies with the Veterans Administration to test **the effectiveness of propranolol** alone and in combination with other antihypertensive drugs. Data analysis is nearing completion and publication of the results is planned.
- A pilot clinical trial on **treatment of mild hypertension** conducted in cooperation with the Veterans Administration has recently been completed. An ad hoc committee reviewing these results and those from other similar studies reached the conclusion that NHLBI should not undertake a full-scale trial at this time.

Epidemiological Studies. Long-term epidemiological studies are also being conducted in an effort to identify persons at risk of developing hypertension.

- The **Epidemiology of Hypertension in the Young** Program is attempting to identify the precursors and correlates of elevated blood pressure in all age groups. This program's main areas of emphasis are genetic and familial studies; "tracking" studies in which blood pressure in children is recorded periodically over time; follow-up studies on factors measured in prenatal and infant studies; studies in children whose mothers had toxemia of pregnancy; and studies of diet, psychological, growth, and other factors which may relate to elevated blood pressures in the young.
- Data are now available from the **Framingham Study,** a prospective study on 5,209 individuals in Framingham, Massachusetts, which in 1977 completed 29 years of follow-up. The study has revealed that hypertension, in addition to its role as a risk factor for heart attack, sudden death, and stroke, is the major

cause of congestive heart failure. One important aspect of this analysis is that it indicates that elevated systolic pressure plays a role equal in importance to elevated diastolic pressure in the development of congestive heart failure. This finding is worthy of further investigation since diastolic pressure had traditionally been considered the more critical of the two blood pressure readings.

Animals Models. In an effort to develop animal models for hypertension, the following steps can be reported:

- During the past year, the NIH Division of Research Services has arranged to introduce three strains of hypertensive rats into its facilities. These strains, the New Zealand, Milan, and Dahl S and R rats, will be bred in colonies and eventually made available to all investigators. NHLBI played a major role in encouraging the establishment of resource colonies of these and other strains.
- Attempts are also in progress to develop nonhuman primate models of essential hypertension.

State of the Science in 1977

Considerably more is known now than in 1972 about the vasodilator and vasoconstrictor systems and their relation to hypertension. Biochemical studies over the past five years have added important new information to our understanding of the pathogenesis of hypertension. Studies on blocking agents have shown that irregularities in the renin-angiotensin system are related to some forms of hypertension; the familial kallikrein studies have linked the excretion of low amounts of kallikrein to elevated blood pressures; and the prostaglandin studies suggest that defects in prostaglandin metabolism may have a genetic component that predisposes test animals to hypertension.

While evidence exists that renin levels are an important factor in most forms of essential hypertension, some hypertensive patients do not show elevated renin levels. In these cases, it is possible that mineralocorticoid activity may be critical. Increased levels have been detected in the urine of spontaneously hypertensive rats. The search continues for new mineralocorticoids in low renin, essential hypertension patients.

All of these findings have added considerably to our understanding of the biochemical events that affect the etiology and pathogenesis of hypertension. Yet more information is needed, and further research in this area is required. Consequently, the Institute is continuing to fund basic research on all aspects of hypertension, including the support of studies on the renin-angiotensin-aldosterone vasoconstrictor system and on the vasodilator system of kallikrein-kinins and prostaglandins.

At the same time, current clinical trials to evaluate the effectiveness of antihypertensive therapy are continuing. Studies of inhibitors specific to the kinin, kallikrein, and prostaglandin hormone systems will go forward, and improved assay techniques will aid in more closely monitoring the effects of these inhibitors on their specific biochemical targets.

The Hypertension Task Force, created to report on the current status of hypertension research, has met frequently during the past year to review and assess progress and achievements and to recommend avenues of needed future effort. Its final report will be completed in the near future. Meanwhile, both new and continuing research efforts will concentrate on the Institute's short-range goal of improving the effective treatment for hypertension, while at the same time increasing the knowledge of underlying mechanisms, so that the long-range goal of prevention of all forms of hypertensive disease can become a reality.

Program Goals: 1978–1982

Better understanding of the physiological systems that control blood pressure and the means by which these systems can initiate and/or exacerbate the developmental process of hypertension could result in a significant reduction in the incidence of hypertension as well as in more effective therapy among those already afflicted. The following basic goals have been established by the Institute as guidelines for research during the next five years:

- Emphasize research on etiology and pathogenesis of hypertension.
- Encourage development of improved meth-

ods and techniques for all aspects of hypertension research.

- Identify important new areas for research emphasis through the Hypertension Task Force activities.
- Broaden the interdisciplinary base for contributions to hypertension research by attracting scientists to this field who traditionally have not been involved or those unaware of the magnitude of their potential contributions if their efforts were directed toward this area of research.
- Complete the Hypertension Detection and Follow-up Program (HDFP).
- Implement effective models of high blood pressure control on a community-wide basis.

Research Activities: 1978–1982

Over the next five years, a steady progress toward realizing the Institute's mission is anticipated as a result of the following research activities.

Continuing research efforts include:

- Clarification of the role of renin as an initiating factor in essential hypertension; the role of mineralocorticoids in hypertension; the role of urinary kallikrein in the pathogenesis of hypertension; and the relation of renal prostaglandin metabolism to hypertension.
- Research on inhibitors of renin and angiotensin.
- Continuation of the Hypertension Specialized Centers of Research Program.
- Further studies on the epidemiology, etiology, pathogenesis, diagnosis, treatment, and prevention of hypertension in the young.

Studies to be implemented:

- Research on the efficacy of the treatment of high blood pressure in the elderly.
- Research programs on central neural control of blood pressure and the effects of hypertension and vasoactive agents on the vasculature. New emphasis will be placed on studies of how the brain participates in hypertension and in blood pressure control.
- Research on inhibitors of kallikrein, bradykinin, and various prostaglandins.
- New research initiatives as recommended by the report of the Hypertension Task Force due to be completed in FY 78.

Studies under consideration for increased support:

- Etiologic studies including research projects to develop chemical antagonists to several physiological hormones which may be involved in the development of high blood pressure.
- Possible expansion of the Hypertension Specialized Centers of Research Program after FY 80.

Schedule

The *Report of the Hypertension Task Force* will be completed in FY 78, and its recommendations for new research initiatives will likely be implemented in FY 79–82.

New research programs on the central neural control of blood pressure and the effects of hypertension and vasoactive agents on the vasculature will be initiated in FY 78 and will continue at least through FY 80.

The Hypertension Specialized Centers of Research Program may be expanded after FY 80.

The HDFP is expected to complete its planned five years of treatment and follow-up of the enrolled 11,900 hypertensive individuals in FY 80. Data analysis will continue through FY 82.

A new clinical trial of the efficacy of hypertension control in the elderly (to be conducted in collaboration with the National Institute on Aging) should begin in FY 79 and last through FY 82.

Community, work setting, and statewide demonstrations of high blood pressure control initiated in FY 77 will continue through FY 82 when they are expected to become self-sustaining through other sources of funding.

Cerebrovascular Disease

Cerebrovascular disease is the third leading cause of death in the United States, after coronary

artery disease and cancer, and represents an enormous personal and public health burden to the nation in terms of the resulting brain damage, paralysis, and death. The basis for most strokes, cerebrovascular disease results when the arteries supplying blood to the brain are blocked or ruptured, thus depriving the brain of needed oxygen and nutrients. The resulting cerebral infarction or ischemic damage accounts for 70 to 80 percent of all strokes, the rest being due to hemorrhage.

The arterial injury is often caused by atherosclerosis and/or high blood pressure in the large cranial arteries or the small intracerebral arteries and may be complicated by thrombosis. Thus, effective control of either arteriosclerosis and/or hypertension would be expected to reduce greatly the morbidity and mortality from stroke. However, the cerebrovascular bed poses its own problems in the pathogenesis and treatment of these diseases.

State of the Science in 1972

Severe hypertension, atherosclerosis, and diabetes were recognized in 1972 as major risk factors for the development of cerebrovascular disease. To predict, ameliorate, and eventually prevent cerebrovascular disease, more knowledge was clearly required about these risk factors, about the complications of thrombosis, and especially about their relationship to the development of cerebrovascular disease.

Consequently, the Institute's research effort to understand more about the etiology and pathogenesis of hypertension, diabetes, atherosclerosis, and thrombosis was and still is directly applicable to cerebrovascular disease.

Three other major needs were recognized in 1972 as important in the overall effort to control cerebrovascular disease: epidemiologic studies to clarify the incidence of cerebrovascular disease in the United States; clinical trials to study the effect of risk factor intervention on the development of cerebrovascular disease; and the development of new instrumentation to aid in specifying the degree, type, and site of vascular lesions.

In 1972, the lack of animal models for the development of chronic atherosclerosis, hypertension, and cerebrovascular disease was impeding progress against all of these diseases. Colonies of such test animals could enable researchers to study the effects of hypertension and atherosclerosis on the cerebral vessels as well as on the development of vascular lesions in the brain.

Goals Through 1977

The major goal set by the NHLBI in 1972 in its determination to control and prevent cerebrovascular disease was:

- To decrease the incidence of stroke through studies of the pathology and pathogenesis of cerebrovascular disease.

The Institute took on the responsibility for research on the underlying vascular mechanisms of stroke, while the National Institute of Neurological and Communicative Disorders and Stroke was primarily responsible for programs on those aspects of stroke that dealt with brain injury and its consequences.

Accomplishments Through 1977

The most encouraging and hopeful trend in cardiovascular disease is the continuing decline in mortality, a decline noted for cerebrovascular as well as other heart and blood vessel diseases. Between 1970 and 1976, there was a 20.4 percent decrease in the age-adjusted mortality rate for strokes (Figure 4). While there are no doubt many factors influencing this favorable circumstance, it seems apparent that the overall program of the Institute, especially its new emphasis on hypertension control, has contributed to these tangible results.

Research accomplishments described in the sections on arteriosclerosis and hypertension bear directly on progress against cerebrovascular disease. In addition, the following activities should be noted:

- Information is being collected on the **incidence, prevalence, and predisposition** of populations to cerebrovascular disease and stroke. Disease-related histories have been collected during the Lipid Research Clinics prevalence studies, supported by the Arteriosclerosis Program, and from the 29-year Framingham Study. The Hypertension Detection and Follow-up Program (HDFP) is also mon-

itoring for stroke as part of its attempt to reduce morbidity and mortality resulting from hypertension.

- **Noninvasive diagnostic procedures and techniques** are being developed and perfected. One instrument uses ultrasound to visualize atherosclerotic plaques and narrowing of the main blood vessels to the brain.
- **Cerebrovascular atherosclerosis in non-human primates** has been experimentally produced for the first time, and this model should be a useful tool for future study of early vascular pathology in these vessels.

State of the Science in 1977

The key to control and prevention of cerebrovascular disease is understanding the etiology and pathogenesis of hypertension, atherosclerosis, and diabetes, the three major risk factors associated with stroke and the complications of thrombosis. Progress in these areas is described in detail in the sections on arteriosclerosis and hypertension.

Recently, greater interest in diabetes as a risk factor in cerebrovascular disease has been evidenced, and intensified research in this area is now in progress.

Epidemiologic studies to identify environmental factors and personal characteristics which might influence the risk of stroke have been in progress in the long-term Framingham Study, the Lipid Research Clinics, and the Hypertension Detection and Follow-up Program. The results of these studies should have positive value for the control of cerebrovascular disease.

Meanwhile, efforts at influencing the habits of Americans, particularly to control hypertension, cholesterol levels, and cigarette smoking, are being made under the Multiple Risk Factor Intervention Trial. This program is designed to lower the risk of developing arteriosclerosis, hypertension, and thus, of heart attack and stroke.

Definite progress has been made in the development of animal models for the experimental study of arteriosclerosis, hypertension, and stroke. A resource colony of stroke-prone rats is now available for research and non-human primate models are ready for the investigation of chronic vascular changes resulting from hypertension and arteriosclerosis; cerebrovascular atherosclerosis has been produced in non-human primates. These positive steps should open the way to better understanding of these diseases in the future.

There continues to be a need for a detailed assessment of cerebrovascular disease, particularly a direct comparison between pathological, functional, and pharmacological phenomena in the vascular beds of other parts of the body as compared with the cerebrovascular bed. Although the trend toward lowered mortality rates from cerebrovascular disease is a cause for optimism, much more research is required to achieve the Institute's goal of further decreasing the incidence of stroke, a major threat to the life and well-being of hundreds of thousands of Americans.

Program Goals: 1978–1982

The mission of the NHLBI in the area of cerebrovascular disease is to elicit further information on the pathogenesis of cerebrovascular disease and to enhance programs that will accomplish this goal. Thus, the major goals of the program are to:

- Gain further basic understanding of the pathogenesis of cerebrovascular disease.
- Encourage increased research activity exploiting the recent development of animal models of cerebrovascular disease.
- Develop noninvasive instrumentation to facilitate the diagnosis and observation of disorders of the large vessels supplying the brain.

Research Activities: 1978–1982

In the next five years it is hoped to double or triple the research activity supported by the Institute in this area. The research opportunities afforded by the recent development of animal models of cerebrovascular disease will also be exploited. Specifically, the program plans:

Continuing research efforts:

- Basic etiologic and pathogenic studies relevant to cerebrovascular disease.
- Epidemiologic studies to identify environmental factors and personal characteristics which predispose persons to increased risk

of stroke and to vascular chronic brain injury. Such studies are being conducted in the Framingham Study, the Lipid Research Clinics, the Multiple Risk Factor Intervention Trial, and the Hypertension Detection and Follow-up Program. Progress of these studies will be carefully monitored.

- Information, demonstration, and education programs aimed at influencing Americans to reduce or eliminate those factors—such as uncontrolled hypertension, high cholesterol levels, and cigarette smoking—known to be associated with the development of cerebrovascular disease. This is a goal of the Multiple Risk Factor Intervention Trial now in progress.

Studies to be implemented:

- Expand the program by notifying the research community that cerebrovascular disease is an area of special Institute interest.
- Initiate a program of short-term small grants to encourage preliminary or exploratory research, of an interdisciplinary nature, on the pathogenesis and vascular complications of cerebrovascular disease.
- Request applications to study lesion pathogenesis in particular animal models.

Schedule

Those activities listed under continuing research efforts will continue through FY 82.

The special notice will be issued in FY 79. The program of short-term small grants will begin in FY 81.

Studies in animal models are expected to be expanded in FY 80.

Coronary Heart Disease

Coronary heart disease is the most common cause of death in the United States, accounting for 1.25 million heart attacks each year and chronic illness in over 4 million adult Americans.

A heart attack is a manifestation of coronary heart disease and occurs when the coronary artery is blocked, preventing the circulation of blood to the heart muscle. The result is myocardial infarction, death of that portion of the heart muscle deprived of oxygen and nourishment. The coronary artery blockage is brought about by atherosclerosis, a condition in which fatty and fibrous plaques or thickenings of the arterial linings protrude into the lumen of the blood vessel, narrowing or totally blocking the passageway.

Other important manifestations of coronary heart disease are angina pectoris, a pain usually located in the chest and radiating to the left arm, brought about by decreased circulation to heart muscle; heart failure, an impaired pumping function of the heart, which causes accumulation of fluid in the lungs and other parts of the body; arrhythmias, disturbances of heart rhythm; and sudden death.

State of the Science in 1972

In 1972, information was available on many aspects of the causes, diagnosis, and treatment of coronary heart disease. However, there was a need for further research to resolve basic unanswered questions, the most fundamental of which was why coronary heart disease ultimately manifests itself as heart attack and sudden death. While it was clear in 1972 that ventricular fibrillation, a chaotic disturbance of the heart rhythm, is the final stage before sudden death, no drugs or other effective treatments were available to prevent this condition, except under intensive medical care in the hospital setting.

Coronary artery surgery to bypass a narrowed or occluded segment of a coronary artery was practiced in 1972 as a treatment for angina pectoris, but its value compared with medical management and conventional drug therapy, and its effects on the lifespan and the quality of life of the patient required further research and assessment.

The high frequency of out-of-hospital deaths from coronary heart disease contrasted sharply with lives saved through in-hospital systems of emergency cardiac care, highlighting the need for improved methods of arrhythmia control and cardiac resuscitation to be administered in emergency situations outside hospitals.

Intensified research, both clinical and fundamental, was clearly critical to developing a better understanding of the cause and course of coronary heart disease and for improving diagnosis and treatment.

Goals Through 1977

In 1972, the Institute established the following goals for its program on coronary heart disease:

- To develop a better understanding of the mechanisms leading to symptomatic coronary heart disease.
- To develop improved methods for the diagnosis and treatment of coronary heart disease and for the rehabilitation of the survivors.
- To establish guidelines for the use of coronary artery surgery in the treatment of various forms of coronary heart disease.
- To develop and assess emergency medical care methods for heart attack victims.
- To develop and assess prophylactic treatment with drugs to prevent sudden cardiac death.

To implement these goals the following activities were planned:

- Establish Specialized Centers of Research on Coronary Heart Disease at approximately 12 locations to create the opportunity for comprehensive clinical investigations and closely related fundamental laboratory studies.
- Plan a collaborative national program to establish indications for and effects of coronary artery surgery. The plan included randomized studies to compare surgery versus medical management in carefully defined groups of patients with coronary heart disease.
- Develop and test early care methods and instruments for cardiac patients at risk of sudden death, suitable for incorporating into emergency medical care systems.
- Conduct large-scale clinical trials of antiarrhythmic drugs for long-term prevention in high-risk patients and for immediate administration upon development of heart attack symptoms.

Accomplishments Through 1977

- As a result of clinical research, **hospital mortality from heart attack** has been reduced, as has the **length of the hospital stay.** The in-hospital mortality rate from heart attack has been significantly reduced. Also, within the first week of hospitalization, it is now possible to identify a subset of patients with myocardial infarction who can be discharged within a week or 10 days of admission without adversely influencing their prognosis.
- Research on sudden cardiac death continues to provide a better understanding of the circumstances under which chronic coronary heart disease converts to acute heart attack and death. Today, the wider, more effective implementation of **emergency medical systems**, including cardiopulmonary resuscitation (CPR), is saving lives that otherwise would be lost to out-of-hospital deaths. Approximately 60 percent of patients who die of coronary heart disease die before hospitalization. In one community of about 500,000 inhabitants at least 100 lives are saved annually by new resuscitation techniques alone.

The instructor is using a mannequin to demonstrate the life support techniques used in cardiac arrest as part of a training course for employees of the National Heart, Lung, and Blood Institute.

- The Institute has undertaken a program on **sudden cardiac death and lethal arrhythmias.** Antiarrhythmic drugs are used to prevent ventricular fibrillation, the terminal event that precipitates sudden death. Results from preliminary clinical trials indicate that it may be possible to prevent some fatal arrhythmias with the chronic administration of these agents. Drugs that block the beta-adrenergic system have shown particular promise in this regard. In conjunction with antiarrhythmic drug studies, the Institute is investigating factors that may precipitate sudden cardiac death or convert chronic coronary heart disease into an acute catastrophic illness. This work suggests that the role of the autonomic nervous system and other possible psychophysiologic factors need further investigation.

- The **Aspirin Myocardial Infarction Study** has been initiated by the Institute, following up on an earlier pilot study suggesting that ingestion of aspirin might reduce the incidence of recurrent myocardial infarction. The study has completed its recruitment phase, and a total of 4,524 men and women with a documented history of myocardial infarction have been enrolled. Early record-keeping has begun and indications are that subjects are adhering to the treatment protocol and the initial dropout rate is low.

- Data from the Framingham Study have established a risk factor profile for the 49- to 82-year-old group which combines seven major parameters: blood levels of low density lipoproteins, high density lipoproteins, and triglycerides; systolic blood pressure; enlargement of the left side of the heart; relative weight; and diabetes. Isolating these parameters allows determination of the extent to which an older individual is at risk of developing coronary heart disease. The Framingham Study found that less than 2 percent of the coronary heart disease in its subject population occurred in the 10 percent of the population at lowest risk based on the risk factor profile. Conversely, 30 percent of the coronary heart disease was found in the 10 percent of the subject population whose profiles indicated they were in the highest risk category. If high-risk individuals can be identified early through risk factor profiles such as those used in the Framingham Study, it should be possible to begin therapeutic intervention before coronary heart disease develops or at least before existing disease results in serious heart damage or death.

- The three large-scale clinical trials to evaluate the **effects of risk factor modification** on several cardiovascular diseases—the Hypertension Detection and Follow-up Program, the Lipid Research Clinics' Coronary Primary Prevention Trials and the Multiple Risk Factor Intervention Trial*—bear directly on coronary heart disease prevention. By 1984, we should know the efficacy of manipulating these three major risk factors—high levels of blood cholesterol, high blood pressure, and cigarette smoking—on heart attacks.

- The Institute has launched a specific research effort on **cardiovascular problems of the diabetic.** Although it has been known for some time that cardiac disease is the cause of death in 80 percent of individuals with diabetes, the majority of past studies on coronary heart disease have excluded diabetics from their subject pool.

- Preliminary results of a collaborative study comparing the effectiveness of early coronary artery bypass surgery with intensive medical therapy in the management of the acute stages of unstable angina pectoris indicate that **patients with unstable angina** may be safely treated with intensive pharmacological therapy. Those with persistent pain may be studied by coronary angiography, and those with left main coronary artery obstruction and continued intractable pain may require surgery. Otherwise, prophylactic surgery to prevent a myocardial infarction or death is not necessary and the decision on possible surgery can be made on the basis of the patient's chronic symptomatology.

* See sections on arteriosclerosis and hypertension.

- A large-scale, comprehensive, collaborative clinical trial—the Coronary Artery Surgery Study—is assessing the effects of coronary artery bypass surgery on morbidity and mortality in **patients with chronic coronary heart disease.** Final results from this study should facilitate the development of a more comprehensive picture of the indications for selecting surgery or intensive medical management in these patients.
- **Pharmacological methods for protecting ischemic myocardium** have been developed recently, and the Institute is undertaking a multi-center, collaborative clinical trial to assess the efficacy of these regimens, extensively studied in animal systems.* In ischemic myocardium, local diminution of the blood supply following a heart attack can place an area in jeopardy before permanent, irreversible damage to the heart muscle has occurred. Evidence from animal studies shows that irreversible damage can be reduced by appropriate interventions; this therapy must now be evaluated in man.
- A new technique is in use for viewing the heart via **computer-based movies** before and during intense exercise. This technique facilitates the detection of abnormalities and the diagnosis of coronary artery disease even in asymptomatic patients whose cardiac function is normal when measured at rest. In addition, the new technique makes it possible to assess the degree of functional impairment in patients known to have coronary artery disease and to evaluate the effects of therapeutic interventions. The technique uses a very small amount of radioactive serum albumin which remains in the blood and thus shows the contraction pattern and effectiveness of the heart. These techniques are the result of coordinated efforts of intramural scientists and engineers from NHLBI, the NIH Division of Computer Research and Technology, and the Nuclear Medicine Department of the NIH Clinical Center.
- Another radioisotope test utilizes Thallium 201, which is taken up by normally functioning heart muscle. By comparing the uptake of this radioisotope before and after exercise, areas of underperfused heart muscle can be recognized. This allows for the detection and assessment of medically significant coronary artery obstruction that may be symptomatically inapparent.
- New imaging techniques using radionuclides with very short half-lives make it possible to produce three-dimensional reconstructions of the heart. This process facilitates the quantification of infarct size and *in vivo* assessment of different regions of the heart. Radionuclide imaging techniques also permit plotting of accurate graphs of ventricular blood volume to assess ventricular ejection fractions and to follow changes in these parameters with time or in response to intervention.
- The development of QRS mapping techniques of electrocardiograms has shown the R wave loss and Q wave development are indicative of myocardial necrosis. This technique has been used in both laboratory and clinical settings to detect when ischemic myocardium has been salvaged through therapeutic intervention.
- A recent development of a radioimmunoassay technique for detection of an isoenzyme of creatinine phosphokinase that is released into the blood stream after heart muscle damage facilitates accurate diagnosis of cardiac damage even in the absence of changes in the patient's EKG. This technique permits more sensitive measurement of this isoenzyme. Another technique detects myoglobin, an even earlier although somewhat less sensitive indicator of muscle damage.

State of the Science in 1977

The most important development to be reported is the recent improvement in the death rate from coronary heart disease. Between 1970 and 1976, the age-corrected death rate has decreased 14.5 percent. While the precise causes of this favor-

* See section on heart failure and shock.

able change are not clear, the trend has been a continuous one. A number of significant developments have contributed to this lower death rate, including changes of life style, greater health consciousness, better control of hypertension, decreased smoking, and alterations in diet. However, important developments in understanding and care of disease have undoubtedly played an important role in the better recognition and management of patients with early symptoms of heart disease and in the management of in-hospital acute illness.

There is now clear evidence from several retrospective studies that once heart attack has occurred, it is the amount of heart muscle damage and heart function impairment which become the major determinants of survival, overriding in importance even the three major risk factors—hypertension, smoking, and elevated cholesterol. This evidence further emphasizes the importance of primary prevention of heart muscle damage.

A majority of coronary heart disease deaths still occur before hospitalization. However, more effective emergency care systems are now bringing patients to hospitals more quickly, before their heart muscle is extensively and irreversibly damaged.

Substantial improvement in the ability to diagnose coronary heart disease has been achieved, with the development of such techniques as noninvasive radionuclide detection of myocardial defects, radioimmunoassays to detect chemical changes associated with acute myocardial disease, improved electrocardiographic mapping, and the Thallium 201 stress test for identifying patients with severe coronary artery obstruction.

Coronary bypass surgery has been compared with intensive medical management for patients with unstable angina pectoris. The assessment indicates that, in patients with "impending heart attacks," acute surgery is no more effective in reducing morbidity and mortality than intensive medical management, a result directly applicable to clinical practice.

Promising early results for measures of protecting ischemic myocardium during a heart attack warrant a large-scale clinical trial to test the efficacy of certain pharmacological agents. At the same time, the ability to detect and assess areas of heart muscle where irreversible damage has already occurred, while identifying other areas that are still salvageable, promises to help reduce disability and death due to heart failure and shock.*

Lethal arrhythmias, known to be the cause of half of the deaths from heart attack, are better understood today, and clinical trials of promising drugs are under way to improve the management of chronic and acute arrhythmias.

A variety of rehabilitation programs have been established in recent years to give patients who have survived myocardial infarction an improved sense of well-being, enhance their work capacity, and improve their reintegration into family and community activities. While some of these efforts have been successful, a firmer scientific basis for rehabilitation efforts is needed.

Many approaches against coronary heart disease are being pursued. Future programs will continue to tackle the major unsolved problems of coronary heart disease and, as more basic and clinical data accumulate from the programs already in progress, the Institute will try to move quickly to ensure rapid application of this knowledge. Although significant progress has been made and the death rate statistics are encouraging, we will continue to search for improvements in the management of coronary artery disease, the number one cause of death in the United States.

Program Goals: 1978–1982

The ultimate objective directing the Institute's choice of program goals for the next five years is to further decrease mortality from coronary heart disease. Since it is not possible to quantitate the effective contribution of a specific research program to the impressive saving of lives and productivity, as well as the savings in hospital and rehabilitation costs resulting from the decreased death rate from 1970 to 1975, an unequivocal basis for the assignment of program priorities cannot be established. Accordingly, the essential thrust of already established programs will be continued together with ongoing assessment procedures. In addition, flexibility to pursue promising initiatives not yet identified will be maintained.

* See section on heart failure and shock.

The specific goals through which the Institute plans to further reduce death and disability from coronary heart disease are the following:

- Improve the recognition and assessment of latent coronary artery disease and overt coronary heart disease.
- Improve the therapy of patients with acute myocardial infarction and patients with chronic ischemic heart disease.
- Assess the proper role of coronary artery bypass surgery in the management of ischemic heart disease.
- Assess possible methods for the reduction of the incidence of sudden cardiac death.*
- Develop techniques for reducing the amount of heart muscle irreversibly damaged during the course of myocardial infarction.**
- Develop methods of reducing the incidence of recurrent myocardial infarction.
- Improve rehabilitation of patients with coronary heart disease.

Research Activities: 1978–1982

In order to achieve these program goals, the NHLBI will support research efforts including the following:

- The Specialized Centers of Research (SCORs) on Ischemic Heart Disease will broaden their emphasis to include aspects of coronary heart disease beyond the current major emphasis on acute myocardial infarction. Greater focus will be concentrated on chronic angina pectoris, rehabilitation, and early recognition of patients with coronary artery disease still in the presymptomatic stage.
- Expansion of research emphasizing the recognition of presymptomatic coronary artery disease as a means of identifying those at risk of developing acute and potentially lethal episodes of heart attack and sudden cardiac death. Importance will be placed on techniques such as the combination of radioisotopic assessment of ischemic zones during exercise and a variety of other methods.
- Evaluation of the results of the clinical trial in coronary artery surgery in combination with the recently completed studies on unstable angina pectoris to improve the assessment of indications for, and long-term effects of, coronary bypass surgery.
- Expansion of studies in the area of sudden cardiac death including recognition of high-risk groups, improved understanding of what converts chronic coronary artery disease into an acute ischemic episode including death, and the means of prophylaxis.
- Completion of studies designed to reduce the recurrent rate of myocardial infarction and updating of the assessment of the chronic use of aspirin as a prophylaxis against recurrence.
- Promotion of community surveillance programs to track trends in coronary heart disease morbidity and document changes in risk factors and prevention practices.
- Investigations of environmental factors, such as weather, trace metals, and degree of water hardness which might affect coronary heart disease morbidity and mortality.
- A trial of chronic prophylactic antiarrhythmic therapy in patients as heightened risk for sudden cardiac death, i.e., survivors of an acute myocardial infarction.

Schedule

The Specialized Centers of Research on Ischemic Heart Disease will undergo competitive review for continuation and expansion during FY 80.

The Coronary Artery Surgery Study will have completed patient recruitment, and follow-up of all patients will have been completed by June 1983, with only the final data analysis phase remaining.

The program of research on sudden cardiac death will undergo competitive renewal and expansion in FY 78.

The trial of chronic antiarrhythmic therapy to reduce sudden cardiac death should have patient recruitment completed by December 1980, with patient follow-up complete three years thereafter.

* See section on arrhythmias.

** See section on heart failure and shock.

The Aspirin Myocardial Infarction Study is expected to complete follow-up in FY 80, with only final data analysis remaining.

Further efforts in rehabilitation research and therapy are currently in the planning and feasibility evaluation stage. Though the magnitude of the problem and the importance of solutions are recognized, the extent to which this activity can grow is not yet defined.

Peripheral Vascular Diseases

Peripheral vascular diseases are the result of abnormalities that occur in arteries carrying blood to the extremities of the body, or in veins returning blood to the heart. Hardening of the arteries (arteriosclerosis) occurs as the artery walls become thick and hard, inhibiting the adequate flow of blood. Venous damage results when veins become dilated (varicosities) or inflamed, or are obstructed by blood clots (thrombophlebitis). Together, these conditions comprise the bulk of peripheral vascular disease. They can cause considerable suffering and disability, including organ damage, skin ulcerations, or gangrene, and, in some cases, death.

Patients undergoing major surgical procedures are particularly susceptible to postoperative thromboembolic complications. A substantial fraction of patients undergoing certain types of surgical procedures or who are at prolonged bed rest develop venous thrombi. Statistics suggest that at least 10,000 and possibly as many as 50,000 patients die annually due to complications resulting from blood clots or embolic fragments originating in the lower extremities and traveling to the lungs.

State of the Science in 1972

In 1972, there was limited research effort devoted to peripheral vascular diseases. Surgeons had developed techniques to replace large peripheral, intra-thoracic, and intra-abdominal artery segments with vascular or prosthetic grafts, but little attention was paid to research on disorders of the veins or the medium or smaller branch vessels of the large arteries. Very little was understood of the underlying mechanisms that might lead to peripheral vascular disease, other than arteriosclerosis, and more information was needed on improved diagnosis, therapy, and rehabilitation of patients.

Goals Through 1977

The goals of the NHLBI programs in the area of peripheral vascular diseases in 1972 were to improve diagnosis, therapy, and rehabilitation, and to increase our knowledge of the mechanisms responsible for causing peripheral arterial, venous, and lymphatic diseases. To meet those goals the NHLBI identified and recommended the development of research initiatives in the following areas:

- Development of diagnostic procedures for the early detection of vascular diseases.
- Conduct of clinical, laboratory, and epidemiological research into the causes, diagnosis, and treatment of diseases of the peripheral arteries and veins.
- Identification of the relation of physiology and pathophysiology to clinical manifestations of disease.

Accomplishments Through 1977

During the past five years, progress has been made in research areas pertaining to peripheral vascular diseases.

- Improvements have been made **in assessing the severity of peripheral arterial diseases** with the advent of new ultrasonic, radioisotopic, and radiographic techniques.
- A **new method for detecting small blood clots** in veins has been developed involving a sensitive radioimmunoassay for fibrinopeptide A, a constituent of blood clots. The assay is more specific and more sensitive as an indicator of clotting than other available methods, and clinical diagnosis of peripheral venous thrombosis can now be made more accurately.
- The ability **to replace or bypass irreversibly obstructed lesions** in large major arteries has advanced markedly, and substantial research has also improved our use of such therapy for medium and small sized arteries.

- **Reduction in the incidence of venous thromboembolism** may be achieved through carefully controlled low-dose heparin therapy. The anticoagulant is given before surgery and during the recovery phase until the patient is ambulatory. Since heparin may prevent blood clotting, proper doses must be chosen to avoid excessive bleeding during surgery.
- **Epidemiologic data** on prevalence, incidence, and the effect of risk factors in the development of peripheral vascular diseases are being collected.

State of the Science in 1977

In the past five years, noteworthy advances in the diagnosis and management of peripheral vascular diseases have been reported. These in turn have provided a new awareness of the overall magnitude of the problems associated with these diseases.

Progress has centered on more accurate diagnostic procedures for detecting small venous clots. The use of ultrasonic, radioisotopic, and radiographic techniques improves the ability to assess the severity of peripheral arterial disease.

Considerable interest has been generated in the use of prophylactic low-dose heparin therapy to prevent thrombosis in high-risk patients undergoing major surgery.

There have been recent advances in the surgical replacement or bypass of irreversibly obstructed lesions in large major arteries, and substantial progress using this therapy for medium and small sized arteries.

Epidemiologic data on the prevalence, incidence, and effect of other cardiovascular risk factors on the risk associated with the use of oral contraceptives and other agents have significant clinical implications.

In spite of these research advances, however, the complex nature of peripheral vascular diseases is poorly understood. Further research is required to identify the underlying causes of these disorders —the role of neural control of vascular tone, the mechanisms of action of arterial wall smooth muscle, and the pathogenesis of peripheral atherosclerosis.

Emphasis on continued improvement of surgical grafting techniques for small vessel grafts is also needed, as well as attention to the problems of peripheral vascular diseases in diabetic patients. Long-term follow-up of current surgical graft procedures is important, as well as continued attention to better diagnostic methods. Peripheral venous disease—varicose veins—remains a subject of considerable importance, yet little research is being done in this area.

Epidemiologic research should continue to assess what role certain risk factors, such as cigarette smoking and other habits, play in the onset of peripheral vascular disorders.

Significant progress has been made in the ability to diagnose, treat, and prevent peripheral vascular diseases, and certain factors linked with potential risk of developing arterial or venous abnormalities have been identified. But more needs to be known about how and why these disorders occur, and why certain individuals appear to be at high risk of developing these disabling conditions. The potential benefits of greater knowledge of basic mechanisms in this area are yet to be realized and improved clinical management of peripheral vascular diseases can be anticipated only with the acquisition of such knowledge.

Program Goals: 1978–1982

The Institute's broad goal in the area of peripheral vascular disease for the next five years is to improve techniques for the diagnosis and treatment of peripheral arterial and venous diseases.

Specific goals over the next five-year period are to:

- Develop more effective noninvasive methods of evaluating the severity of peripheral arterial diseases, suitable both for the assessment of symptomatic patients and for the recognition of latent arterial diseases.
- Improve the management of patients with peripheral arterial diseases, with particular attention to the long-term effects of arterial grafts and the improvement of graft techniques for smaller arterial vessels.
- Encourage greater research effort on the causes and treatment of peripheral venous diseases.

Research Activities: 1978–1982

To achieve these goals, the Institute plans to pursue the following research initiatives during the period 1978–1982.

Continuing research efforts include:

- Further development of noninvasive techniques for detecting and quantifying atherosclerosis in the clinical setting.

Studies under consideration for increased support include:

- Improvement in techniques for the grafting of smaller caliber peripheral arteries, including the development of synthetic graft materials.
- Evaluation of the long-term reliability of prosthetic graft materials now in use.
- A greater research effort in peripheral venous disease, for example, varicose veins.

Schedule

The program of development of noninvasive methods for the detection and quantification of atherosclerosis has undergone competitive review and minor expansion in FY 77. It is anticipated that substantial growth following competitive review in FY 80 will be warranted because of the rapid advances in technology and in its translation to important aspects of patient care.

The targeted activities for the development of small caliber arterial grafts and for the long-term comparative assessment of existing large caliber grafting techniques would require, when feasible, program expansion in approximately FY 79 or FY 80.

Arrhythmias

There are many types of arrhythmias (heart rhythm disturbances). Some are not indicative of heart disease and cause no ill effects. Others may be a manifestation of heart disease and may even be associated with an increased likelihood of sudden cardiac death.

State of the Science in 1972

In 1972, lethal arrhythmias were believed to be causing 50 percent of the deaths from heart attack. It was known, for example, that in the face of a heart attack, ventricular arrhythmias often resulted in ventricular fibrillation and death; the role of such arrhythmias in out-of-hospital sudden death was suspected but not known. The means of assessing risk factors and identifying populations at risk were of limited effectiveness and availability. Chronic preventive therapy against ventricular arrhythmias was also ineffective.

The mechanism of action of lethal arrhythmias was incompletely understood. More needed to be known about the electrophysiology of arrhythmias associated with ischemic or coronary heart disease. Antiarrhythmic drugs, which had been in use for years, were of some effectiveness in reducing arrhythmias, but their effectiveness in saving lives was unknown; furthermore, most had serious and undesirable side effects. A better understanding of the fundamental characteristics of arrhythmias associated with ischemic myocardium (tissue deprived of an adequate blood flow) was needed. Clinical studies, together with computer-aided analysis of recorded electrocardiographic data, were needed to assess the possible efficacy of therapeutic regimens.

In 1972, the Institute, in accord with the recommendations of the National Heart and Lung Advisory Council and the Heart and Blood Vessel Disease Panel, emphasized the need for research to improve the understanding and prevention of lethal arrhythmias. Research needs on arrhythmias ranged from a better understanding of the fundamental mechanisms to the facilitation of clinical investigation.

Goals Through 1977

Based on these research needs, the program goals of the NHLBI in 1972 were to advance basic knowledge and improve prevention, detection, and treatment of arrhythmias.

To achieve these goals, the Institute identified six specific program initiatives to be implemented during the period 1972-1977:

- Research on the overall problems of sudden cardiac death.
- Research on the fundamental mechanisms of arrhythmias, particularly those associated with ischemic heart disease.

- Clinical studies, of various populations, designed to develop descriptors of those at increased risk.
- Research on the significance and prognosis of conduction disturbances.
- Specialized Centers of Research on Ischemic Heart Disease to provide a multidisciplinary clinical and basic research environment for studying various aspects of heart disease, including sudden cardiac death and rhythm disturbances.
- Workshops on the prevention of sudden cardiac death emphasizing clinical trials of potential approaches to antiarrhythmic prophylaxis.

Accomplishments Through 1977

Substantial gains have been made in the Institute's attempts to achieve its program goals.

- It is now established that **ventricular fibrillation** is the overwhelming cause of sudden cardiac death.
- It has been learned that ventricular fibrillation can occur in persons with coronary heart disease without acute myocardial infarction and result in sudden death. Of those patients who are resuscitated from out-of-hospital ventricular fibrillation, only a minority are found to have evidence of an acute myocardial infarction.
- **Conduction disturbances** have become better understood through several long-term studies. Although all the answers are not yet in, many conduction disturbances are far less ominous than had been thought. It is likely that the subsequent death of such patients is more often the consequence of their advanced heart disease and eventual heart failure than of the conduction disturbance.
- It is now recognized that **premature ventricular contractions** (PVCs) in the absence of detectable heart disease carry no unfavorable prognosis. This allows those patients who have PVCs but are otherwise free of disease to be reassured of their good health.
- The limitations of the widely used **antiarrhythmic drugs** are now better recognized—their limited effectiveness in controlling arrhythmias and their side effects—and it is now known that control of arrhythmias cannot be automatically equated with prevention of death.
- **New antiarrhythmic agents,** which are becoming available for clinical investigative use, offer considerable promise of being effective against ventricular rhythm disturbances. Although these new agents are effectively controlling such arrhythmias, their role in the more commonly encountered arrhythmias and in the management of ischemic heart disease in general still remains to be defined.
- Methods have now been developed for **blood level measurements** of many of the currently used and studied antiarrhythmic drugs. This permits the correlation of effectiveness and safety of these drugs with a patient's blood levels rather than with the orally administered dose.
- Major improvements have been made in **computer-based rhythm analysis systems,** thus facilitating clinical studies of arrhythmias and their treatment.
- The **mechanisms** which give rise to arrhythmias are now better understood. While major gaps in understanding remain, the roles of slow and fast calcium currents, of reentry rhythms, and of other factors are becoming increasingly clear.
- Major advances have occurred in the introduction into emergency medical systems of **new techniques of emergency care,** including the recognition of, and emergency therapy for, high-risk arrhythmias.

State of the Science in 1977

The role of ventricular arrhythmias in the cause of sudden death is recognized. The commonly used 24-hour ambulatory monitoring devices reveal such ventricular arrhythmias with considerable frequency, both in the presence and absence of recognized heart disease. The limitations of currently available

antiarrhythmic agents, in terms of efficacy as well as associated side effects, pose further problems. While it is clear that, for the patient with ventricular arrhythmias and no detectable evidence of heart disease, no therapy is warranted, the proper course of action for the patient with recognized heart disease and arrhythmias remains a problem.

With this in mind, the Institute has established a large-scale clinical trial to test the possible efficacy of chronic beta-adrenergic blocking agents in survivors of myocardial infarction with a goal of reducing subsequent cardiac death. Preliminary small-scale trials with related drugs have shown promising results in this clinical setting.

Concurrent with this clinical trial, assessment continues of other new antiarrhythmic drugs which may have more specific antiarrhythmic activity and greater efficacy in the control of arrhythmias.

Research at the fundamental level is also continuing. As we gain better understanding of the mechanisms of arrhythmias, new gaps in our understanding are identified which are critical for the development of truly effective prevention and therapy. Investigations are in progress to determine the relationship of changes in ion exchange and metabolism at the cellular level, as a possible explanation of both the cause and the consequence of arrhythmias. Research concerning ion fluxes across cardiac cell membranes is under way, and the possible association of the "slow" calcium current with certain rhythm disturbances is under study. The possible role of the autonomic nervous system in the development of arrhythmias is attracting considerable attention, and a workshop is being planned to determine the future course of study in this area.

Large-scale clinical studies are currently being conducted to determine whether clinical and laboratory parameters can be developed to predict sudden death and to assess the condition of patients with intraventricular conduction defects. Both efforts are concerned with the development of reliable means of predicting risk in population subgroups.

Electrocardiograms are being systematically recorded on magnetic tape and annotated to allow testing of the effectiveness and reliability of computer systems designed to recognize and describe arrhythmias automatically.

The understanding of lethal arrhythmias has substantially improved since 1972. Progress has been made, and the new knowledge is beginning to decrease the number of deaths. However, there is need for increased effort to understand the fundamental processes of electrical rhythm and conduction disorders and to develop methods of prevention and acute therapy.

Program Goals: 1978–1982

As is so often the case in man's search for new knowledge, solution of a problem usually generates more questions than answers. When knowledge of the variety and characteristics of arrhythmias was vague, research focused principally on collecting and classifying descriptive information. Now that sophisticated monitoring systems routinely provide these data, the focus of NHLBI research is on improving the understanding of, and the means to prevent, lethal arrhythmias. Consequently, the broad goals of the Institute now are to define the fundamental processes of electrical rhythm and conduction disorders and to develop methods of acute and chronic preventive therapy.

Specific goals of the Institute over the next five years are the following:

- Develop an improved understanding of the mechanisms whereby arrhythmias arise.
- Develop methods of chronic prophylactic therapy, using pharmacological agents, to prevent sudden cardiac death.
- Assess the role of pacemakers in the management of various conduction disturbances and define the indications for their use.
- Achieve a better understanding of the significance of rhythm disturbances commonly found in long-term, ambulatory monitoring of electrocardiographic rhythm to permit better clinical management.
- Develop more effective methods for the recognition of those at heightened risk of sudden cardiac death.

Research Activities: 1978–1982

In order to achieve these goals, the Institute plans to pursue the following research areas during

the next five years:

- Studies of sudden cardiac death, with particular attention to identifying those at heightened risk and to characterizing the fundamental mechanisms which convert chronic coronary artery disease into an acute process.
- Elucidation of fundamental mechanisms of rhythm disturbances.
- Studies to determine the significance of various rhythm and conduction disturbances in the general population and their correlation with risk.
- Clarification of the significance of various conduction disturbances and evaluation of the role of pacemakers in such circumstances.
- Improvement in automated methods for reading long-term (24-hour) rhythm monitoring tapes for the assessment of risk and therapeutic efficacy in ambulatory individuals.
- Development and distribution of standard reference rhythm monitoring tapes showing a variety of dysrhythmias to permit the comparative assessment of automated devices for reading heart rhythm tapes.
- Assessment of the possible therapeutic efficacy of chronic antiarrhythmic therapy with beta-adrenergic blocking agents.

Schedule

The targeted program on lethal arrhythmias and sudden cardiac death will have undergone competitive renewal and hopefully expansion in FY 78: this program is anticipated as warranting further competitive renewal in FY 81.

The chronic antiarrhythmic trial for the reduction of mortality from coronary heart disease will have completed recruitment and will be in large measure completed in FY 82.

The development of standard annotated tapes for rhythm analyzing devices will have been completed in FY 80 and available for general use.

Targeted activities to assess the significance of rhythm disturbances in the general population and to enhance the understanding of conduction disturbances and the role of pacemakers will require appropriate program expansion by FY 80.

Heart Failure and Shock

Heart failure most commonly occurs when heart muscle damage is so excessive that the heart cannot pump enough blood to accommodate the body's needs. The damage can be caused by a variety of diseases.

Shock may be a complication of heart attack, stroke, hemorrhage, or other illness; it involves inadequate blood pressure and insufficient blood perfusion. If left untreated, shock can precipitate irreversible damage to major organs and can lead to death.

State of the Science in 1972

The presence and severity of heart failure and shock are related to the amount of heart muscle *irreversibly* damaged in the course of a heart attack. Damaged muscle does not contract and ultimately forms a scar. In 1972, it was postulated that the amount of heart muscle that would go on to irreversible damage in the course of a heart attack was generally not fixed at the onset of the attack. It was believed that significant areas of heart muscle were deprived of adequate blood flow and were in jeopardy, but had not undergone irreversible damage. One of the pressing needs at that time was to test this hypothesis and to develop a means for minimizing damage to this jeopardized but not yet irreversibly damaged heart muscle. As a corollary to this, it was necessary to develop methods for quantifying accurately the extent of heart muscle that had undergone irreversible damage, and for identifying and treating the area that was potentially salvageable.

Many of the biochemical derangements at the subcellular and systemic levels associated with heart failure and shock were known, but a great deal more was yet to be learned. True cardiogenic shock—shock due to heart muscle damage (in contrast to shock from other causes such as hemorrhage or insufficient hydration)—was fatal in over 90 percent of cases. Pharmacological methods were sometimes effective in raising the blood pressure during shock, but rarely effective in saving life. Prevention of heart failure and shock was dependent upon early treatment of some forms of heart disease, or better yet, upon prevention of heart disease itself.

In recognition of the magnitude of this problem,

the National Heart and Lung Advisory Council in 1972 recommended that studies of heart failure and shock receive high priority.

Goals Through 1977

The goals set by the Institute in 1972 were:

- To minimize heart failure associated with, and following, heart attack by enhancing the survival of damaged heart muscle.
- To develop and apply a variety of therapeutically effective, safe, and reliable cardiac assist and total replacement devices together with the supporting diagnostic and monitoring information.

Accomplishments Through 1977

Several important advances have been made in this area:

- **The ability to reduce damage to heart muscle** following a heart attack has been improved by a variety of means. For example, extensive animal studies have shown promising results from various pharmacological agents which diminish the work load of the heart; improve blood flow and enhance diffusion to ischemic areas; diminish swelling (and thereby enhance perfusion) and provide essential metabolic substrates. Several of these techniques have been brought into limited clinical use, although most are still at the investigational stage. Intra-aortic balloon pumping, a form of mechanical circulatory assistance,* has been studied as a means of protecting the myocardium, but is more commonly used as a part of the therapy of cardiogenic shock.
- **Fundamental research on ischemic heart muscle** has improved our understanding of basic mechanisms and biochemical processes and our ability to estimate the period over which muscle may be ischemic before it undergoes irreversible change.
- **Techniques have been developed for assessing with increasing precision the amount of heart muscle undergoing damage.** Such techniques include sequentially mapping the electrical signals from the heart at various sites over the chest; measuring the amount of enzymes released by damaged heart muscle into the blood; identifying normal or damaged myocardium by radioisotopes which selectively go to one or the other; and measuring the extent and timing of the movement of various portions of the heart, utilizing x-rays, the echocardiogram, or radioisotopes.
- The pharmacological therapy of true cardiogenic shock has not improved substantially since 1972. However, the use of **mechanical circulatory assist devices,** such as the intra-aortic balloon, has permitted some patients to undergo further evaluative study and definitive surgical correction—and to survive—all of which would have been impossible in the absence of such mechanical assistance.
- **Earlier and more vigorous treatment of heart attack** by conventional means appears to be diminishing the frequency and severity of heart failure and shock during the course of a heart attack.
- **Methods for measuring the performance of the heart** have been developed, suitable for use in the critically ill patient. This permits the therapist to more precisely determine the optimum therapeutic dose of drugs selected for therapy and to more closely approximate the desired physiological and therapeutic effects.

These developments, ranging from better understanding of the subcellular function of heart muscle to clinical studies and radioisotope technology, have provided some progress over the past five years in the prevention and management of heart failure and shock.

State of the Science in 1977

Research since 1972 on heart failure and shock has contributed significant therapeutic benefits and has identified knowledge requirements which now

* For more information on cardiac assist devices, see section on circulatory assistance.

represent the basis for current and future research activity.

Some pharmacological methods for protecting ischemic myocardium have been sufficiently developed that the Institute is now undertaking a multicenter, collaborative clinical trial to assess their efficacy. At the same time, the search continues for other promising therapies by means of fundamental and applied research.

The program continues to obtain information about the pathophysiology of ischemic myocardium, to seek improved methods of therapy, and to develop better methods for quantifying and protecting ischemic myocardium. Progress is notable in all of these areas. In addition, the Specialized Centers of Research on Ischemic Heart Disease are conducting multidisciplinary clinical and fundamental research designed to reduce death and disability associated with ischemic heart disease, including in particular heart failure and shock.

Until quite recently heart failure and shock were the most dreaded complications of acute myocardial infarction because available methods of intervention could seldom prevent death. While these entities remain a formidable challenge to the physician, Institute-sponsored research programs have made significant progress in the last few years. This progress provides a basis for developing more effective prevention and treatment of heart failure and shock.

Program Goals: 1978–1982

In the next five years the Institute plans to further define mechanisms, improve diagnostic techniques, and develop methods for the prevention and treatment of heart failure and shock of cardiogenic origin. Specific Institute goals are to:

- Elucidate the fundamental, biochemical, and cellular mechanisms involved in myocardial ischemia and gain a better understanding of the systemic effects of cardiogenic shock.
- Develop methods for protecting ischemic myocardium and for preventing the conversion of reversible ischemic tissue to irreversible infarcted and scarred myocardium.
- Develop methods for quantifying the extent of ischemic myocardium to aid the assessment of therapeutic efficacy and patient management.

Research Activities: 1978–1982

Research activities for the next five years will focus upon the fundamental biochemical derangements associated with myocardial ischemia. As this research progresses and new knowledge is developed and validated, the NHLBI program in this area will focus increasingly on bringing potential therapeutic interventions to fruition and on decreasing morbidity and mortality.

Continuing research efforts include:

- Investigation of the biochemical and cellular mechanisms involved in myocardial ischemia.
- Elucidation of the systemic effects of cardiogenic shock.
- Development of methods for the protection of myocardial ischemia and for preventing the development of irreversibly infarcted and scarred myocardium.
- Development of clinically applicable methods for quantifying the extent of myocardial ischemia.

Studies to be implemented include:

- A collaborative clinical trial on protecting ischemic myocardium will assess the ability of several pharmacological interventions to reduce the amount of myocardial ischemia which develops into irreversibly scarred tissue during the process of acute myocardial infarction.
- Assessments of the applicability, precision, and limitations of several promising techniques for determining the extent of myocardial ischemia in post-infarction patients.

Schedule

The program on fundamental research on protecting ischemic myocardium is undergoing competitive renewal in FY 78. Further growth will be warranted in approximately FY 81, with a greater emphasis upon therapeutic interventions. By FY 79, it is anticipated that more uniform methods of as-

sessing therapeutic interventions in animal models will have been developed so that they may serve as a basis for program expansion in this area by FY 79 or FY 80.

Research on methods of quantifying ischemic myocardium in the clinical setting underwent competitive renewal in FY 77. Further review in FY 80 is planned to determine whether program expansion is warranted.

The Collaborative Clinical Trial on Protecting Ischemic Myocardium entered into its design phase in FY 77; it is anticipated that patient recruitment will begin in FY 78. At that time, the number of participating institutions may be expanded so that an increased patient population can provide earlier answers in this important program. It is envisioned that these studies will continue at least through FY 81.

Congenital and Rheumatic Heart Diseases

Congenital and rheumatic heart diseases are serious illnesses that can cause premature death or impair the quality of life from childhood to adulthood. Each year, about 25,000 children are born with defective hearts; of the 6,500 of these children who die annually, approximately half are less than one year old. Rheumatic heart disease affects approximately 100,000 children and 1.7 million adults in America, with more than 13,000 of them dying each year.

Congenital heart disease refers to the condition that results from the improper formation of the heart during prenatal life. The causes of these malformations are largely unknown. However, several factors appear to be associated with their development, including the mother's use of drugs such as thalidomide during pregnancy; maternal diabetes; genetic predisposition to heart malformations; the mother's contracting German measles (rubella) in the first three months of pregnancy; and certain genetic diseases (such as Down's syndrome).

Rheumatic heart disease is the result of damage to the heart and its valves caused by rheumatic fever, a complication of streptococcal throat infection. Its effects may go unnoticed for years. Some children suffer rheumatic fever with no evidence of valvular damage during the initial attack. The damage may have occurred, however, and may not be detected until a later date. For this reason, prevention of rheumatic heart disease by prompt diagnosis and treatment of streptococcal throat infections are a matter of high priority.

State of the Science in 1972

In 1972, echocardiography was just beginning to gain prominence as a noninvasive means of determining heart defects in newborns, but no method existed for detecting these defects in developing fetuses. Open heart surgery, in use at that time for adults and older children, was beginning to be used to correct heart malformations in infants and newborns and was proving successful for most of the more common defects. Surgical techniques for repair of more complicated defects were still largely inadequate, although success at complex repairs was beginning to be reported at a few centers.

Since streptococcal throat infections precede the occurrence of rheumatic fever, the correct diagnosis and prompt treatment of these infections are important means of reducing the incidence of rheumatic fever and, in fact, hold the key to prevention. By 1972, the practice of combating streptococcal infections with penicillin had been in use for over 20 years, and the number of cases of rheumatic fever had declined dramatically from the pre-penicillin era, attesting to its preventive potential. Penicillin, however, had no value in repairing the damage to heart valves once it had occurred. Persons suffered congestive heart failure as a result of rheumatic fever-induced heart valve damage. Techniques for replacement of injured valves with artificial devices were in extensive use in 1972, but there were still problems associated with the prosthetic valves available at that time. Further improvements were necessary.

In 1972, the Institute identified a number of important areas of need: to stimulate research on the embryology and pathology of congenital heart disease; to continue making improvements in surgical repair techniques and in noninvasive instrumentation; and to emphasize education for the public as well as the physician regarding diagnosis and treatment of throat infections.

The highest priority, however, was given to prevention. To achieve this goal, it was recognized

that more understanding about the basic nature of these illnesses was required.

Goals Through 1977

The general goals developed by the Institute for the congenital and rheumatic heart disease programs were:

- To perform clinical and fundamental research on the causes of congenital heart disease and to improve methods of diagnosis and treatment.
- To identify the immunologic impact of streptococcal infection associated with rheumatic fever, and to develop and evaluate therapy for the suppression of such immunologic responses.

Accomplishments Through 1977

Specific accomplishments during the past five years have contributed significantly to progress in these areas. Examples of these accomplishments are:

- Improvements in the **use of echocardiography,** proven beneficial in the noninvasive diagnosis of older children, have shown special merit in the management and diagnosis of congenital lesions in newborns and young infants. With such devices as a real-time multiple-crystal ultrasound scanner, the spatial locations of the chambers of the heart and the major heart valves can be visualized. With this new equipment, it is often possible to determine how the heart valves are functioning as well as which chambers of an infant's heart are enlarged and how the enlargement responds to medical treatment.
- Interest in research on the causes and effects of cardiovascular defects in the fetus is responsible for continued **efforts to develop animal models** with a high incidence of congenital heart lesions. These animal models are rare, but through current research efforts in various centers, new groups of animals have recently been identified. Such models are becoming available so that investigators can pursue research into the alterations in embryological development of the fetus and can develop techniques for intrauterine diagnosis of congenital lesions.
- Several **drugs** have been discovered that **inhibit the synthesis of the hormone prostaglandin.** Tests are being conducted to determine whether these drugs have benefit for the treatment of such conditions as patent ductus arteriosus, a congenital abnormality in which a vessel connecting the pulmonary artery to the aorta fails to close. The condition is often present in premature infants. In preliminary trials, closure of the abnormal shunt was responsive to prostaglandin-inhibiting drugs. Tests are continuing to determine whether this technique is of true therapeutic benefit and whether it may be used in lieu of surgical closure.
- Experiments on newborn and young puppies have provided valuable data on the **effects of drug therapy in the newborn animal.** By analyzing the amount of digitalis in the bloodstream, relationships between the dosage of the drug and its effect in the infant's treatment have been determined. As a result of these and other studies, it has been shown that human infants and newborns require a higher concentration of digitalis and other drugs per kilogram of body weight than that required by older patients. This knowledge provides another way to determine effectiveness levels for infant drug therapy and offers additional protection against toxic reactions from incorrect dosages.
- Studies of the **biological activities of the streptococcal cell,** focusing upon the cell capsule, the cell wall, and the cytoplasmic membrane, have provided potentially useful data. The antigen that is responsible for the immunological responses associated with rheumatic fever appears to be located in the cytoplasmic membrane. Studies such as these hold promise of new understanding of the pathogenesis of rheumatic fever.

State of the Science in 1977

The sophisticated surgical procedures available in 1977 make it possible to save the lives of more

individuals with congenital or rheumatic heart disease than ever before. Data provided by several cardiac surgical centers have been used to develop new guidelines for the most appropriate time to correct congenital heart defects. Techniques are so refined that even premature infants with heart defects have improved chances of survival after surgery. Valuable as these surgical corrective techniques are, they are expensive and delicate and only part of the solution to congenital and rheumatic heart disease.

The Institute has supported research efforts on the causes and prevention of congenital and rheumatic heart disease. A colony of dogs with congenital heart defects is providing an experimental base for studying genetic factors in the development of heart abnormalities. In other experiments, animals ranging in development from the intrauterine fetus to the adult are being used to test the relative effectiveness and toxicity of therapeutic drugs, to develop and test prosthetic heart valves in older animals, to evaluate new surgical interventions, and to determine the biological action of these diseases.

Significant progress has been made in improving the diagnosis and therapy of congenital heart disease, and in improving animal models for the study of embryological development, for investigating possible genetic factors in the development of heart abnormalities, and for developing techniques for intrauterine diagnosis of congenital heart lesions in the fetus.

The Task Force on Prevention and Treatment of Cardiovascular Disease in the Young is completing its work and is in the process of preparing a Task Force report. The charge to the Task Force was to assess the opportunities and needs for research in childhood as it applies to congenital heart disease, acquired heart disease, and precursors of heart disease in the adult. Experts in the areas of fetal and neonatal cardiology, genetics, congenital heart disease, both surgical and medical, electrophysiology, atherosclerosis, hypertension, and behavioral psychology serve on the Task Force. The group has assessed all aspects of potential prevention of heart disease beginning with the development of the heart and completing with the impact of human development on diseases of the heart in infancy, childhood, and adulthood.

Program Goals: 1978–1982

The economic value of prevention of congenital heart defects and rheumatic heart diseases versus their cure is one of the best examples of cost-effectiveness in medical care today. Knowledge of this fact and the need to provide still better means to diagnose and treat those already afflicted are the concepts underlying the Institute's research program during the next five years.

During that period, the Institute's research program will be directed toward achieving the following three goals:

- To better understand the etiology of congenital heart defects.
- To improve surgical techniques for repair of defects and noninvasive techniques for diagnosis and treatment of patients with congenital heart defects.
- To educate the public and practicing physicians in the diagnosis and treatment of throat infections, particularly those of streptococcal origin.

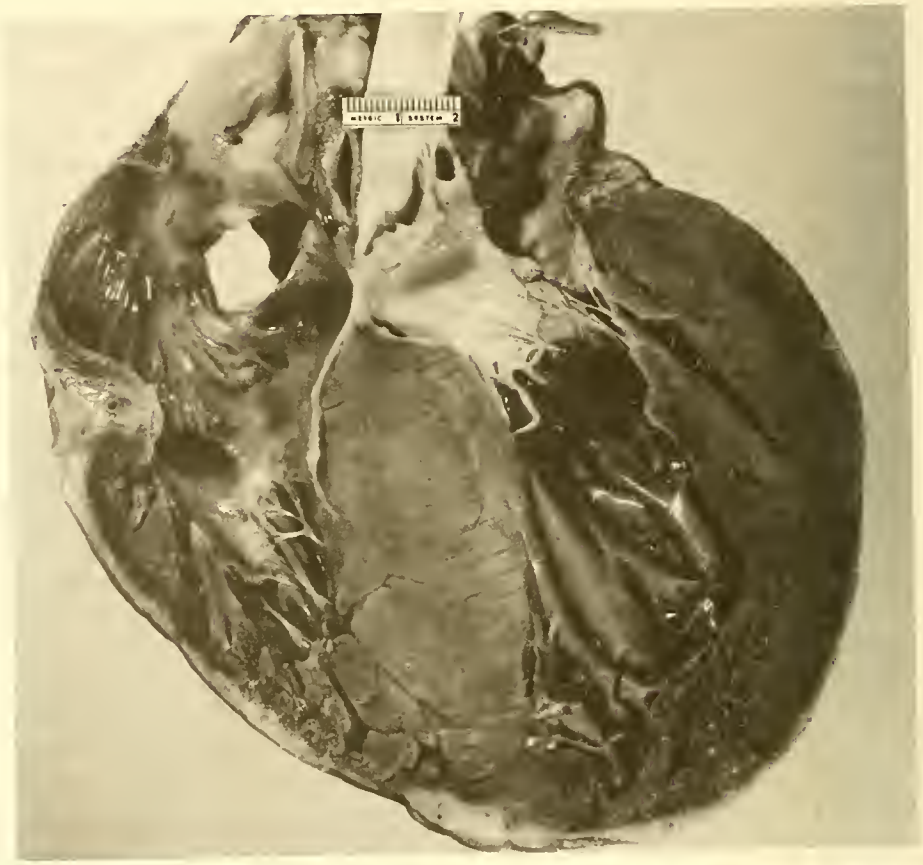
Research Activities: 1978–1982

Over the next five years, the Institute's continuing research efforts will include programs designed to:

- Develop improved techniques for the recognition of congenital and rheumatic heart diseases.
- Develop improved methods for preventing the occurrence and recurrence of rheumatic heart diseases.
- Facilitate the long-term follow-up of patients who have received the benefit of surgical repair for specific congenital heart defects.
- Determine the efficacy of pharmacological agents for the management of certain forms of congenital heart diseases.

Schedule

It is anticipated that this general area will grow during the next five years. The recommendations of the Task Force on Heart Disease in Childhood, available in FY 78, will help to guide development of the Institute's programs for FY 79.



Prior to the discovery of the diagnostic technique of ultrasound, conditions such as hypertrophic cardiomyopathy were difficult to diagnose. The view of the opened heart illustrates the asymmetric thickening of the ventricular septum. The photomicrograph of cardiac muscle cells in the ventricular septum displays marked disarray of the muscle cells. The normal parallel arrangement of cardiac muscle cells is shown in the photo on the right.

Cardiomyopathies and Infections of the Heart

Cardiomyopathies are disorders of the heart muscle that result from a variety of causes, many of which are unknown. In some cases, the abnormalities may be barely symptomatic and hardly discernible, while others may be associated with substantial heart failure, irregularities of heart rhythm, and sudden death.

Infections of the heart may involve the heart muscle (myocarditis), the interior wall of the heart (endocarditis), or its exterior surface (pericarditis).

Although the roles of toxic substances, viral infections, and immunological phenomena have been widely recognized for some time as important in the development of cardiomyopathies, in many cases the causes of these disorders are little understood.

State of the Science in 1972

In 1972, cardiomyopathies were beginning to be recognized with increasing frequency. It was not clear whether the increase was due to availability of better diagnostic methods or whether some forms were appearing more commonly. In addition, there was little solid available information to document the actual incidence, prevalence, or geographic distribution of these diseases.

Bacterial endocarditis, which had been almost uniformly fatal before the advent of antibiotics, was seen less frequently, and a substantial majority of those afflicted were surviving, though often with significant heart and peripheral organ damage. However, new forms of infection, often due to unusual organisms, were becoming prevalent in patients who had not previously had infections. Among those were cancer and transplantation patients receiving certain types of chemotherapeutic agents known to suppress immunological mechanisms. Viral infections of the heart continued to be associated with this group of heart diseases, but their true incidence and importance were unclear.

Goals Through 1977

As cardiomyopathies and infections of the heart were of varied and ill-defined causes, the Institute saw the need for further investigation into the nature of these disorders. Therefore the following broad goal was set:

- Improved diagnosis of cardiomyopathies and greater understanding of the etiology of the various cardiomyopathies and infections of the heart.

Accomplishments Through 1977

- **Improvements in noninvasive diagnostic instrumentation,** especially the echocardiograph, have led to the recognition of certain cardiomyopathies with increasing frequency, particularly asymmetric septal hypertrophy, mitral valve prolapse syndrome, and those associated with conduction and rhythm disturbances.
- The **role of certain viral diseases** in some forms of myocarditis has been recognized, although the etiology of myocarditis generally remains obscure.
- **Alcohol** has been associated with a toxic cardiomyopathy and its manifestations clarified. The effect of alcohol on heart muscle function and structure has been better assessed.
- There is increasing evidence that **heart muscle function of the diabetic patient** is different from normal individuals and this has become a focus of research.
- Through clinical studies and some animal studies, it now appears that certain individuals may have a **hereditary predisposition** to cardiomyopathies. A hereditary form of cardiomyopathy is being studied in an animal model. Morphometric changes in organelles, extracellular spaces, and membrane systems have been identified during the course of the disease.
- Major strides have been made in cardiac transplantation, an experimental therapy for a variety of cardiac diseases, including cardiomyopathies. At least one-year survival is now achieved in over 60 percent of all cardiac transplantation cases.

State of the Science in 1977

Since 1972, advances have been made toward achieving the Institute's goal of better understanding the underlying causes of cardiomyopathies and infections of the heart. The causes of most cardiomyopathies still remain obscure, but a number of factors have been identified as causative agents and their specific roles clarified. Alcohol has been identified with a toxic cardiomyopathy and its effect on heart muscle function and structure better understood; the role of certain viral diseases in some forms of myocarditis has been made clearer; and a hereditary predisposition to some cardiomyopathies has been demonstrated through clinical and animal studies.

Improvements in diagnostic noninvasive instrumentation have led to the increased frequency in recognition of certain cardiomyopathies. The heart muscle function of the diabetic patient as compared with normal individuals is receiving more attention. Cardiac transplantation, though still an experimental procedure, has been extending the lives of patients with cardiomyopathies and other cardiac disorders.

Cardiomyopathies and infections of the heart are beginning to receive more attention. The causes of most cardiomyopathies still remain obscure, but a number of factors have been identified as causative agents and their specific roles clarified. Considerable research growth is expected in this area.

Program Goals: 1978–1982

The goals of this program area over the next five years are:

- To further clarify the causes of cardiomyopathies.
- To develop more effective methods for diagnosis and treatment.

Research Activities: 1978–1982

To achieve these goals, the following research activities are planned.

Continued research efforts:

- Develop techniques for the recognition and management of cardiomyopathies and assess their prognostic significance.
- Elucidate the causative factors and mechanisms in cardiomyopathies.
- Develop improved methods for the recognition, treatment, and future assessment of myocarditis of various forms.

Studies to be implemented:

- A workshop to assess the needs and opportunities for research in cardiomyopathies and infections of the heart.

Schedule

Moderate program growth in all program areas is anticipated through FY 82. The planned workshop will develop recommendations concerning areas of research need and the potential benefits of targeted programs in these areas.

Circulatory Assistance

Circulatory assistance is the use of mechanical systems to augment or replace the pumping function of the heart. Such mechanical assistance can take the form of blood pumps to replace the natural heart (the "artificial heart") or to bypass a diseased ventricle (the left ventricular assist device—LVAD). Lesser degrees of circulatory assistance can be achieved by providing a pump-like action through the synchronous expansion and contraction of a balloon in the aorta or through the synchronous squeezing of the lower extremities. Both of these techniques are designed to diminish the arterial pressure when the heart is ejecting blood and to raise the arterial pressure after ejection to augment perfusion throughout the body. Circulatory assist devices are in varying stages of development; some, such as the intra-aortic balloon, have been in use for a considerable period of time, while others are in developmental stages. Devices are being designed for emergency short-term use measured in hours or days, for periods of several months, or for longer term periods.

State of the Science in 1972

In 1972, the heart-lung machine, a circulatory assist device employed during open-heart surgery for periods up to a few hours, was in routine use. The intra-aortic balloon (inserted into an artery in the

groin and threaded into the aorta to relieve the work load of the heart by synchronous expansion and contraction) had been in use for several years, at first only as a short-term attempt to reverse shock in patients unresponsive to other forms of therapy. However, the circumstances under which the device was effective had yet to be defined.

Experimental efforts to implant artificial heart and left ventricular assist devices were being made in animals. However, the studies were fraught with technical problems—blood clotting, lack of long-term reliability of the units, size of the devices, heat generation, infection at the site of percutaneous leads—together with substantial logistical problems associated with their testing and assessment.

Despite these problems, by 1972 a totally implantable, four-chambered artificial heart had been developed and implanted for a brief period in calves.

Goals Through 1977

Recognizing the anticipated value of circulatory assist devices, the Institute in 1972 set forth the following goals:

- To develop and assess therapeutically effective, safe, and reliable cardiac assist and total replacement heart devices for supporting or taking over the work load of the heart.
- To develop the instrumentation and techniques for the assessment of cardiovascular performance.

However, as progress was made and experience gained, the goals established in 1972 underwent some evolution. The primary thrust of circulatory assist research shifted to left ventricular assist devices with proven reliability for extended periods of use; a total artificial heart became a secondary and more remote goal. Greater emphasis was placed upon electrical engines for energizing such devices (though these require continuous energy supply or recharging of batteries); permanently implanted nuclear energy sources were given a diminished priority.

Targeted instrumentation efforts on the part of the Institute focused upon the development of noninvasive methods for detecting, characterizing, and quantifying atherosclerosis. Throughout the Institute's programs, however, numerous instrumentation developments and techniques for the assessment of cardiovascular performance continued to take place and enjoyed high priority.

Accomplishments Through 1977

- **Intra-aortic balloon pumping** is now in relatively common clinical use. While, by itself, it does not save the lives of those with cardiogenic shock associated with myocardial infarction, in some cases it permits diagnostic studies that otherwise could not be undertaken. Similarly, it is used in some patients who have marginal or inadequate function of the heart in the peri-operative period of open-heart surgery.
- **A pneumatically driven left ventricular assist device** has passed extensive bench and animal testing and is now undergoing investigative short-term testing in man.
- **Toward the goal of long-term left ventricular assist devices,** major advances have been made in increments of engine efficiency and total system reliability, diminished size of components to be implanted, the development of mechanically actuated pumps, materials fabrication, and pump configurations to achieve greater blood compatibility.
- **Pneumatically actuated total artificial hearts,** which replace an animal's normal heart, have now been implanted in calves for periods in excess of four or five months in several laboratories. The calves thrive until they outgrow the pumping capacity of the artificial heart.
- As part of the Institute's **experimental instrumentation program,** substantial advances have been made toward the detection and display of arteriosclerotic lesions that protrude no more than one or two millimeters into the arterial lumen of major peripheral arteries; these techniques are now coming to clinical investigative use.
- **Applications of noninvasive instrumentation,** such as echocardiography, radioisotopic assessment of cardiac function, and computer reconstruction of x-ray images of the heart showing both cross sections and motion, have

been discussed elsewhere in this report.*

- Considerable allowances have been made in the development of **materials** which have the requisite blood compatibility and mechanical properties to make them suitable for circulatory assist and other cardiovascular device applications.

State of the Science in 1977

Today, several laboratories have exceeded four-month survival times for calves with artificial hearts. These animals, tethered to an external energy source, exercise on treadmills and demonstrate normal behavior, including normal rates of growth. Extensive bench and animal studies with the left ventricular assist device have permitted the initial clinical investigative use of this device in man for periods up to ten days.

Current efforts are directed toward refining components and total systems for heart augmentation or replacement. Although these efforts now emphasize circulatory assist devices, all such advances are of fundamental value and of critical importance for the achievement of a total artificial heart. Thus, substantial efforts are continuing on: further development and testing of long-term efficient engines of various types with high reliability; pumps suitable for mechanical rather than pneumatic actuation with flow patterns designed to minimize stasis and thrombus formation; materials with increasingly satisfactory blood compatibility and physical characteristics; percutaneous leads for energizing and recharging of electrical engines; and total systems design.

The knowledge and experience gained from efforts to refine circulatory assistance devices for emergency and other short-term applications are expected eventually to make the goal of long-term assistance or replacement feasible.

Progrram Goals: 1978–1982

Depending on the extent to which cardiac function is compromised, circulatory assist devices may be required to relieve, in varying degrees, the work load of the heart or to perform the entire pumping function in place of the heart. The kinds of devices suitable depend not only on the degree of cardiac function which must be restored but also on the timespan during which such life-saving support is required. Thus, the broad goal of the Institute in this program area is to develop and test, in priority order, short-, intermediate-, and long-term circulatory assist devices for clinical use.

Specific goals include:

- Develop and test, for circulatory assist systems, components such as pumps, engines, and control systems.
- Develop and test biocompatible materials suitable for circulatory assist and other cardiovascular device applications.
- Develop and extensively bench and animal test circulatory assist devices, particularly of the left ventricular assist device type.
- Conduct clinical trials for assessing the efficacy of, and defining the clinical indications for, left ventricular assist devices.
- Support the research and development of other circulatory assist devices.

Research Activities: 1978–1982

Targeted efforts will focus on the development and testing of implantable system components and systems suitable for intermediate- and long-term use. Specifically, the following research activities will be supported during the next five years.

Continuing research efforts include:

- Development of pumps which lend themselves to mechanical and hydraulic actuation since intermediate- and long-term implantable devices require other than pneumatic actuation.
- Development of electrically energized engines rather than radioisotope-energized engines, and of methods of transmitting electrical energy into the body of percutaneous leads or electromagnetic transmission.
- Assessment of materials showing promise for adequate blood compatibility and appropriate mechanical properties for long-term

* See section on coronary heart disease.

implantation requirements.

- Studies of the fundamental characteristics that define blood compatibility of materials.
- Validation of the long-term reliability of devices for clinical investigative use through detailed bench testing and extensive animal studies.
- Clinical studies of short-term devices.

Studies under consideration for implementation:

- Clinical studies with completely new devices suitable for intermediate- and long-term use (many months to years).

Schedule

Based on a comprehensive review of this program area, studies in intermediate-term pumps, energy systems, energy-transmitting devices, and further physical testing of biomaterials were launched in late FY 77. These efforts should lend themselves to consolidation of effort in approximately FY 80. By FY 79, projects dealing with a prototype thermal engine, either electrically or radioisotopically energized, will have been narrowed down to a single candidate engine.

As clinical studies of intermediate-period implantable devices become feasible in FY 81–82, moderate increments in cost may become necessary.

LUNG DISEASES

Diseases of the lung constitute a major national health problem that, for some disorders, is of increasing dimensions. Chronic lung diseases continue to increase steadily as important causes of death and disability in the United States. Lung diseases annually account for well over 100,000 deaths and cost the economy almost $20 billion. Chronic respiratory diseases completely or partially disable millions of Americans of all ages.

Accordingly, the NHLBI program in lung diseases comprises a multifaceted approach to improving our understanding of the causes of respiratory diseases and of the processes that underlie their development; discovering and developing earlier and more precise detection of abnormalities associated with these disorders; and improving therapeutic measures.

Many occupations pose a high risk for the development of lung disease. By wearing air supplied hoods, sandblasters above protect their lungs against inhaling the dusty atmosphere in a large steel fabrication yard.

The following paragraphs describe this multifaceted approach in the context of the areas which constitute the Institute's lung diseases program: structure and function of the lung; emphysema and chronic bronchitis; pediatric pulmonary diseases; fibrotic and immunologic lung diseases; respiratory failure; and pulmonary vascular diseases.

Structure and Function of the Lung

The lack of an adequate base of information about the structure and function of the lung in health and disease is a major barrier to finding solutions to many specific lung disease problems.

The lung is no longer viewed as a simple mechanical organ alternately expanding and contracting to draw in or expel air. Rather, we now know that in addition to its ventilatory function, the lung is a complex organ comprised of many different types of cells, acting and interacting in concert, and accomplishing a variety of hormonal and metabolic functions that may affect not only the lungs but the body as a whole.

Any subtle change in structure or function of these interrelated parts may trigger disease. For this reason, it is essential that research on fundamental mechanisms involving molecular biology, biochemistry, immunology, endocrinology, and cell biology be stimulated in order to understand more about the etiology and pathogenesis of all of the major lung diseases. The insights gained from fundamental research are necessary if we are to open new possibilities for prevention, early diagnosis, and treatment of lung diseases.

State of the Science in 1972

An important and dramatic shift in emphasis in pulmonary research was begun in 1972 when a decision was made to change the major focus of research from the physiological to the cellular and biochemical level.

In 1972, a multidisciplinary Task Force was asked to assess the magnitude of the public health problem posed by respiratory disease, and to evaluate the state of knowledge of particular lung diseases at that time. A major change in direction of research was recommended. It was the overwhelming conviction of the scientific experts that any advances in combating emphysema, chronic bronchitis, pediatric pulmonary diseases, fibrotic and immunologic lung diseases, respiratory failure, and pulmonary vascular disorders would be severely hampered and would be based upon an uncertain foundation unless more was understood about the structure and function of the lung, particularly its cellular and biochemical complexity.

Past pulmonary research had focused on studies of the physiology of the lung—functional capacities of the lung and thorax relating to ventilation, distribution of air and blood, diffusion of gases, and mechanical characteristics of the airways and air sacs that serve as the interface for the entry of oxygen into the blood and tissues of the body, and the exit of carbon dioxide. While this research approach had yielded much valuable information about normal lung function and the patterns of dysfunction in various diseases, it told us nothing about fundamental causes. What was missing was basic information on the cellular and biochemical levels in the lungs, information that would provide the essential underpinning for improved diagnosis, prevention, and treatment of all diseases of the lung.

Recent advances in molecular biology, biochemistry, and immunology had been so rapid as to be called revolutionary, yet none of this new knowledge and technical skill had been brought to bear on lung problems. For example, it was known that the lung is rich in collagen and elastin. Together they form the geometric and structural framework of the lung. But little biochemical detail was available about these proteins, what controlled their synthesis and breakdown, and what specific roles each played in the functioning lung. Yet emphysema was known to be a disease characterized by destruction of lung tissue. The possible relationship between either or both of these proteins to emphysema was unclear at that time. Immunologic lung diseases were known to show abnormalities in collagen metabolism, but little basic information on collagen synthesis and degradation was available.

The lung was known to be a complex organ composed of many different types of cells, some with cilia, others allowing for gaseous exchange, others specializing in secretion of mucus, lipids, or proteins. But little was known of the specific func-

tions of the different classes of cells and tissues, the quantities, composition, and mechanisms of development of these cellular components, their chemical precursors, turnover rates, or their possible variations with age, sex, and environmental influences.

Bronchial mucus was known to be an important factor in the lung's defense mechanisms, and excessive secretion of mucus was associated with serious diseases like chronic bronchitis, cystic fibrosis, and asthma. Yet little information was available on its structure, synthesis, or physiochemical characteristics.

The cilia in the bronchial tree were poorly understood in terms of structure and function, yet this information was crucial to understanding lung clearance and host defense mechanisms against foreign particles and substances.

As a result of these and other gaps in our fundamental knowledge of lung structure and function, particularly on the cellular and biochemical level, in 1972, a decision was made that progress against lung diseases could not be expected unless clinical observations were related to basic biochemical mechanisms in lung tissue. This could only be accomplished after a thorough understanding was gained of cell biology, biochemistry, immunology, molecular biology, and physiology of the lung.

Goals Through 1977

To stimulate the scientific community to change its research direction and focus, a number of new goals were formulated and new research approaches immediately encouraged:

- Investigator-initiated research in the areas of metabolism, cellular biology, and defense mechanisms of the lung.
- Targeted research addressed to topics not adequately covered by investigator-initiated research.
- Multidisciplinary approaches to foster cooperation between basic scientists and pulmonary specialists.
- Workshops designed to attract basic scientists not previously involved in lung research.
- Seminars at national and international meetings to acquaint basic scientists, especially biochemists, physical chemists, immunologists, and cell biologists, with unsolved problems and challenges in lung research.

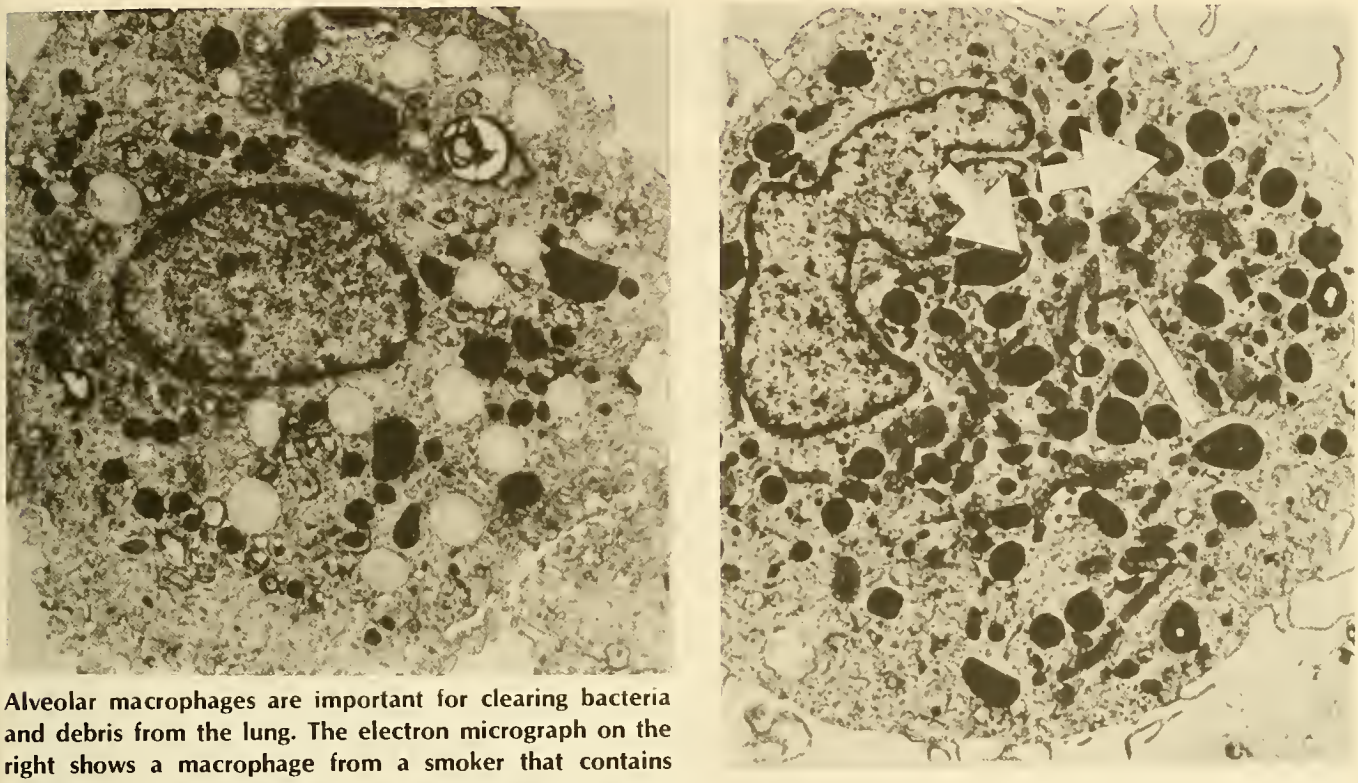
Accomplishments Through 1977

The redirection of emphasis from the physiological to the cellular and biochemical approach has paid off handsomely. Since 1972, many new findings have been reported on the structure and function of the lung, and exciting new avenues for future research have opened up. Especially important is that these developments can be related directly to specific lung diseases, particularly emphysema, respiratory distress syndrome of the newborn, cystic fibrosis, and pulmonary fibrosis. These leads hold great promise for the ultimate control and prevention of pulmonary disease. Some of these advances can be summarized as follows:

- Using enzymatic techniques to disperse lung tissue into separate viable cells, **some success has been achieved in culturing a few of these cell types in laboratory dishes.** Of particular interest is the isolation and growth in cultures of **Type II alveolar epithelial cells.** These cells play a role in repair of the injured lung and may replace alveolar Type I cells. In addition, the Type II cells are thought to be the site of synthesis of the secretion of surfactant, a substance essential in preventing collapse of the alveoli. In newborns with respiratory distress syndrome (hyaline membrane disease), the immature lungs of these infants are deficient in surfactant. Thus, basic research on Type II cells holds the promise of elucidating this disorder, especially concerning abnormal surfactant synthesis.
- **Lung fibroblasts,** one of the specific cell types in the lung that produce collagen, **have been grown in tissue culture.** Their pattern of synthesis has been found to be similar to that in the lung itself. At least four distinct types of collagen are synthesized by animal lung tissue. These have been found to be biochemically similar to collagen from other parts of the body, for example, skin and cartilage, but the distribution of different types of collagen may vary in different parts

of the lung. When diseases such as pulmonary fibrosis develop, this may be caused by a change in the distribution of the different types of collagen. These findings are an important step toward understanding the components of connective tissue, their distribution in the lung, and their modification in diseases of the lung such as pulmonary fibrosis and hypersensitivity pneumonitis.

- **Lung elastin fibers have been analyzed for their amino acid content.** Two amino acids, valine and proline, have been found to be 10 to 20 times more abundant in elastin than in any other structural protein. This opens the possibility for the development of a specific quantitative assay for elastin that will allow it to be traced through its entire history of synthesis, fiber formation, enzymatic digestion, and turnover. In diseases like emphysema, there is a loss of elasticity of the air sacs (alveoli), obviously pointing to some breakdown in elastin. Thus, basic research on elastin holds the key to a deeper understanding of the lung abnormalities that accompany emphysema.
- New information is now at hand on the **interactions of two of the major structural proteins of lung connective tissue**—collagen and elastin. A high molecular weight precursor of elastin is proelastin, which cleaves to form tropoelastin. It is generally accepted that this molecular species is the precursor to insoluble elastin. Preliminary data suggest that collagen may have a protective effect on the cleavage of the high molecular weight protein proelastin, pointing to a potentially significant interaction between the two main structural proteins.
- A new program has been initiated to study the **biochemistry of lung proteoglycans,** another major component of lung connective tissue. The proteoglycans are composed of protein and complex polysaccharides. The role of proteoglycans in lung disease has received scant attention although their potential importance in fostering association between other connective tissue elements has led to speculation that these components are important determinants of normal lung structure and may be altered in the pathogenesis of lung disease. For example, proteoglycan-rich extracellular matrix, because of its insolubility, may serve a protective function by excluding potentially destructive molecules such as proteases, which can digest protein. Additional data are needed to test these concepts.
- Recent studies have shown that **alveolar macrophages of smokers with pulmonary fibrosis contain kaolinite particles,** an aluminum silicate present in cigarette smoke. Alveolar macrophages are important in clearing bacteria and debris from the lung. These studies add scientific substance to the known harmful effects of cigarette smoking.
- **A causative agent has been isolated for one type of hypersensitivity pneumonitis (pigeon breeder's disease).** The purified antigen is a glycoprotein and is now being used as a research tool to investigate the underlying mechanisms of this disease.
- **A lung growth-promoting** factor has been isolated that may prevent the development of respiratory distress syndrome in infants born prematurely and with immature lungs. The substance has been isolated from the urine of pregnant women. When injected into fetal lambs later delivered prematurely by Caesarian section, the growth-promoting factor prevented development of the respiratory distress syndrome; the lungs of these lambs were more mature structurally than lungs of lambs of the same age not receiving the injection.
- **New techniques have been developed in animals for measuring clearance from the respiratory tract of inhaled particles, toxic substances, and mucus** by ciliated cells. Such clearance is an important function which can be impeded in many pulmonary diseases characterized by excessive secretion of mucus or secretion of abnormal mucus. The techniques have been developed to the point where they can now be applied to man. The



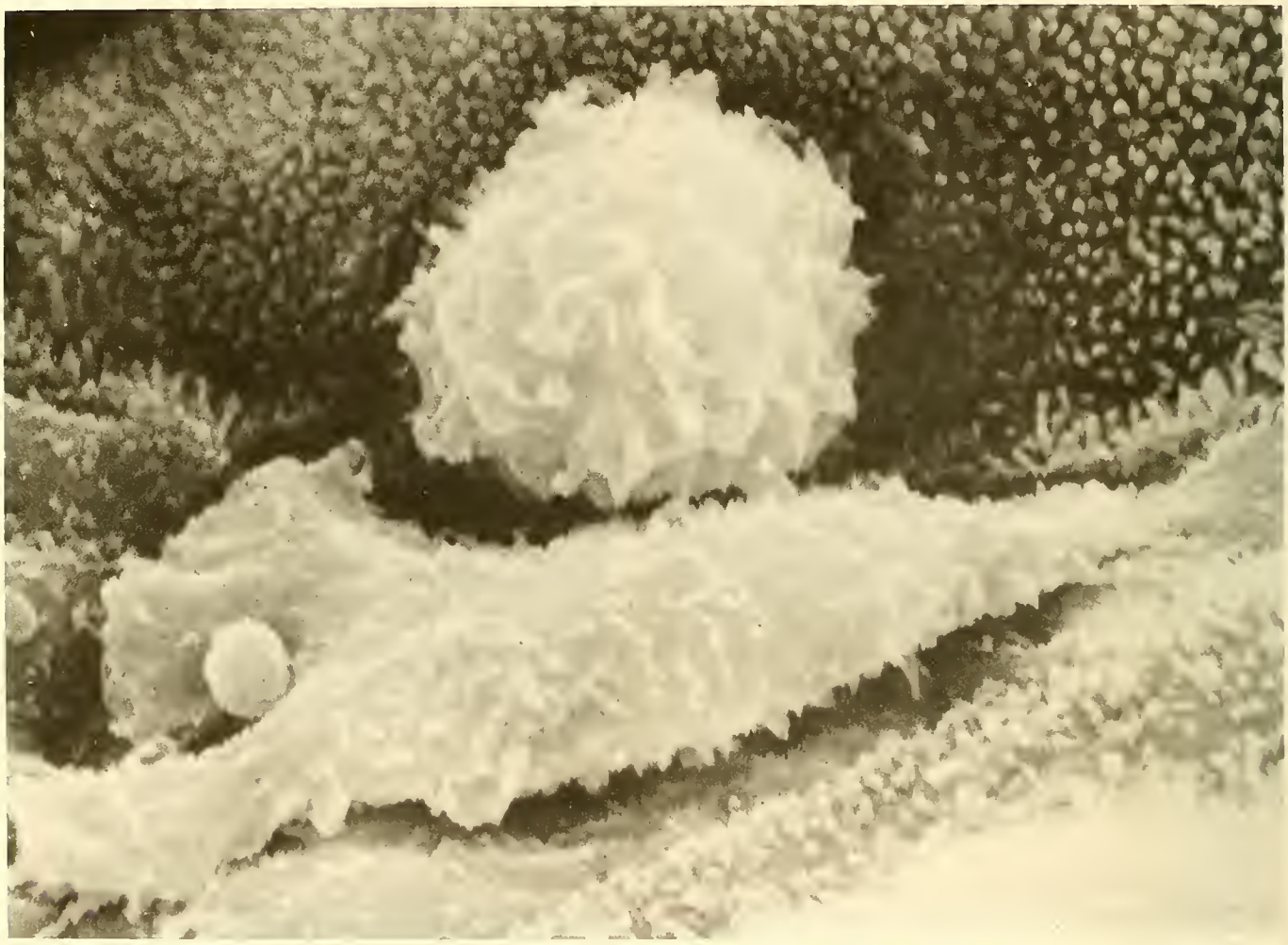
Alveolar macrophages are important for clearing bacteria and debris from the lung. The electron micrograph on the right shows a macrophage from a smoker that contains deposits of kaolinite particles. The electron micrograph on the left is from a nonsmoker and contains no kaolinite particles.

new methodology makes possible the measurement of the velocity of mucus transport by the ciliated epithelium of the airways, collection of mucus for physicochemical analysis, and measurement of transtracheal water and ion fluxes.

- **A new role for the lung in maintaining blood pressure** at normal levels is suggested by the finding that lungs can inactivate bradykinin, a substance that tends to lower blood pressure, and can convert angiotensin I to angiotensin II, one of the most potent hypertensive substances known. One of the enzymes responsible for this chemical conversion has been located on the membrane of a specific cell type, the endothelial cell, which lines blood capillaries. Since all blood from the heart must pass through the lungs for oxygenation on its way to the rest of the body, this means that pulmonary vessels may be important regulators of blood pressure, not only in the lungs but in the entire systemic circulatory system. This adds a potential new dimension to our understanding of the regulation of pulmonary and systemic blood pressure.

State of the Science in 1977

We are much further along in our understanding of the structure and function of the lung than we were in 1972. Significant progress has been made in isolating and growing several lung cell types in tissue culture, and new insights into their functions have been gained. But more knowledge is needed. A major unsolved problem is the identification of isolated or cultured lung cell types. Current methods rely on electron microscopy, a time-consuming technique of identification. Newer and simpler methods for identifying a variety of cell types are required for further progress to occur.



Scanning electron micrograph of two alveolar macrophages. The macrophage at the bottom is about to devour a foreign particle.

A new concept of the lung as an endocrine organ is emerging. Substances passing through the lung can become altered or substances secreted by the lung can later act on target organs elsewhere in the body. Since all blood from the heart passes through the lung on its way to the body, any hormone secreted by lung cells could affect the whole organism. The finding that the lungs can inactivate bradykinin suggests an important role in maintaining blood pressure levels in the pulmonary vessels. This raises the possibility that other substances might be processed or metabolized by the lung, and this is an important new area for future investigation.

Progress continues to be made in assessing pulmonary function on the physiological level. New tests to assess gas flow, gas exchange, tissue elasticity, and surface tension have been developed and can now be used to determine the individuals at risk of developing emphysema and chronic bronchitis, and to evaluate the effects of different methods of therapy. The new tests are also being used to elucidate immunological mechanisms in experimental animals and patients.

In 1972, we knew very little about the structure and function of the lung on the cellular and biochemical level. Today, in 1977, a much more sophis-

ticated view of the lung has emerged. It is a complex organ with diverse cell types, functioning not only in gas exchange, but in defense of the whole organism and in a variety of metabolic and hormonal activities. As we learn more about the fundamental properties of the different cell types of the lung and their interactions with one another, and as lung structure and function in healthy and disease states become better understood, we can feel confident that the gaps in our basic knowledge will become fewer, and that significant progress will be made in understanding the etiology and pathology of these diseases. Such basic information is the necessary foundation for the translation of research results into health care applications.

Program Goals: 1978–1982

The overall goals of the Institute in this sphere are to increase understanding of the normal structure, biochemistry, immunology, cell biology, and physiology of the developing and adult respiratory system, and to determine how these are altered prior to clinical onset and during the course of pulmonary disease.

The specific goals by which this mission will be accomplished are as follows:

- Determine the structural and functional characteristics of, and the interrelationships among, various types of lung cells, their modification in diseases, and their response to injury.
- Characterize the structural components—collagen, elastin, proteoglycans, and basement membrane—of the normal lung and the changes associated with specific lung diseases.
- Characterize the endocrine, immunologic, and other nonrespiratory functions of the lung and their modification in disease.
- Determine the physiologic factors controlling ventilation and transport of gases, and how adjustments are made to increased oxygen need during normal stress situations (such as exercise and high altitude) and in pulmonary disease.
- Use physiologic principles to develop techniques for assessment of pulmonary function in infants, children, and adults.

Research Activities: 1978–1982

Since 1972, when the orientation of the Institute's program concerned with lung structure and function became inquiry at the cellular and biochemical rather than the physiological level, tremendous advances have been made. Research detailed below will carry forward this progress toward the ultimate goal of decreasing mortality and morbidity due to pulmonary disease.

Continuing research efforts include:

- Development of methods to separate major lung cell types into homogeneous and variable populations and to determine the ultrastructural and biochemical characteristics of individual lung cells.
- Studies of the mechanisms of lung tissue damage and repair.
- Investigations of the role of proteoglycans in lung function and growth, and their modification in emphysema and pulmonary fibrosis.
- Studies of intermediary metabolism of lung, using perfused lung, lung slices, and isolated lung cells.
- Studies of basic lung physiology, the role of chemical, mechanical, and neural mechanisms in the control of ventilation, and the processes of gas exchange in the immature and mature lung in health and disease.
- Development and evaluation of noninvasive techniques to measure pulmonary function in infants, children, and adults.

Studies under consideration for increased support:

- Investigations of the chemical structure, molecular architecture, and biosynthesis of connective tissue components in normal lung: evaluation of differences occurring with age, environmental influences, and specific lung diseases.
- Role of pulmonary membranes in the transport of gases, water, and solutes.

Schedule

It is anticipated that investigations on the role of proteoglycans, development of noninvasive techniques, and studies of the role of pulmonary membranes will be completed before the end of FY 82.

Remaining research activities listed above will continue through FY 82.

Emphysema and Chronic Bronchitis

Emphysema and chronic bronchitis, along with asthma, bronchiectasis, and other similar obstructive disorders, contribute to the national health problems of chronic obstructive pulmonary disease (COPD). Within this group, emphysema and chronic bronchitis are considered the most serious because of their high morbidity and, in late stages of disease progression, their mortality.

After lung cancer and pneumonia, emphysema is the third leading cause of death from respiratory disease. It is estimated that one million individuals suffer from the disease. In emphysema, large spaces appear in the lung as the result of alveolar wall destruction, and the fibers in the thin walls of the air sacs (alveoli) lose their elasticity and tear.

Chronic bronchitis, a condition affecting approximately seven million Americans, is characterized by persistent inflammation of the airways, chronic recurrent coughing, and excess mucus production.

In either disease, most patients have a history of prolonged cigarette smoking and present similar symptoms—breathlessness and cough. Physicians can provide only symptomatic relief to patients with emphysema since by the time they are seen, their disease is usually at an irreversible state.

State of the Science in 1972

In early 1973, a report was issued on the current state of knowledge about emphysema and chronic bronchitis. It was considered imperative that better methods be found for more adequate early detection of both diseases. Such methods, the experts felt, should be simple, reliable, and noninvasive so that they could be widely applied to apparently healthy persons. In addition, it was considered a matter of great urgency to identify those individuals who might for a variety of reasons be at high risk of developing these diseases.

Cigarette smoking was known to be associated with the development of emphysema and chronic bronchitis. Almost all patients with these diseases were heavy smokers, but not all smokers developed severe pulmonary dysfunction. This indicated that other etiologic factors might also be important. There was a primary need to identify the factors in cigarette smoke that produced lung damage, a need to understand how the lung clears itself of particles that are inhaled in cigarette smoke, and a need for prospective long-term epidemiologic studies to determine individual differences in response to the harmful effects of tobacco.

On the basis of the evaluation in 1973, the conclusion was unavoidable that cigarette smoking was unique in its impact on the problem of emphysema and chronic bronchitis. A key question to be answered was whether cessation of smoking could reverse the early abnormalities of lung function.

Some emphysema patients were known to have an inherited defect, manifesting itself in a lack of alpha-1-antitrypsin in blood plasma. When present at normal concentrations, this substance holds protease enzymes in check, substances which have the power to destroy lung connective tissue. Although this genetic deficiency was known, complete knowledge was lacking about the association between the absence of alpha-1-antitrypsin and lung disease.

Goals Through 1977

In an effort to achieve its primary goal in this area—to increase the ability to prevent, diagnose, and treat emphysema and chronic bronchitis—the NHLBI promptly set into motion top priority investigations designed specifically to fill the following program needs:

- Elucidation of the role of host factors in lung disease by conducting epidemiologic studies to identify possible genetic or other markers.
- Development of improved techniques and devices for early detection of reversible diseases and application of new knowledge from studies of risk factors and their control.
- Deeper understanding of the lung abnormal-

ities that accompany emphysema on the biochemical level.

- Initiation of controlled clinical trials to evaluate the efficacy of current approaches to therapy and rehabilitation.

Accomplishments Through 1977

In the past five years, new hope for the ultimate prevention and control of emphysema and chronic bronchitis has been generated by the following impressive research advances, the results of deliberate program efforts on the part of the Institute:

- **New and promising methods for detection of early changes** in lung function have been reported which may prove useful in the diagnosis of emphysema. These tests, when done together, present a profile that helps to identify early airways disease. One example of such a test is the measurement of closing volume (the amount of air remaining in the lungs after smaller airways collapse at the end of expiration). This test detects early changes in small airways which may progress to the symptoms of chronic obstructive disease.
- An important role has been assigned to **proteases and antiproteases** in the pathogenesis of lung disease, especially emphysema, and progress has been reported in understanding how these substances operate. The focus is on elastin fibers; the enzyme elastase and other proteases that can destroy these fibers; and antiproteases—one being alpha-1-antitrypsin—that check the action of proteases. Examples of significant new developments in our understanding of this biochemical system are:
  - **Other antiproteases in addition to alpha-1-antitrypsin** have been identified in lung tissue; these afford protection against proteolytic attack of the elastic fibers of connective tissue. This has led to a broader concept of the role of proteases and antiproteases in the connective tissue biochemistry of the lung. Previously, the focus has been on alpha-1-antitrypsin alone.
  - **Twenty-four molecular variants of alpha-1-antitrypsin** have been described to date. The genetic defect associated with emphysema apparently expresses itself in the synthesis of a variant that differs from the antiprotease in normal individuals by only one amino acid substitution in the primary structure of the protein molecule. Earlier hypotheses had surmised that the genetic defect concerned the carbohydrate portion of the molecule.
  - The crucial defect in emphysema patients who lack normal alpha-1-antitrypsin is **failure of the liver to release a protein variant** of alpha-1-antitrypsin into the bloodstream. The result is a lack of antiprotease activity which may lead to unchecked destruction of elastin fibers in the alveolar walls. In addition, the variant accumulates in the liver, resulting in liver damage.
  - **A synthetic substance possessing antiprotease activity** now opens the way to possible replacement therapy in individuals lacking these substances. However, before such therapy can be used to correct the reduced antiprotease activity in some emphysema patients, toxicity studies must be performed. More information on the metabolic fate of alpha-1-antitrypsin is needed, particularly on the role of alveolar macrophages in the clearance of cellular protease.
- New answers are at hand to the key question whether **cessation of cigarette smoking** can reverse or halt the damage known to occur to lung tissue of smokers. As a person ages, the level of normal lung function decreases at a slow but steady rate, even in nonsmokers. In cigarette smokers, however, this aging process proceeds at a much faster rate. When smoking is stopped, the rate of decline of function begins to parallel that of nonsmokers. Thus, while the harmful effects of cigarette smoking are not erased entirely, the steep downward course of lung function is halted, and the rate of aging and loss of lung function follows the same path as that of

non-smokers.

- **Epidemiologic studies** have identified new risk factors in the development of emphysema and chronic bronchitis. Particular attention is now being given to the interaction of all of these factors at the onset of disease. In addition to cigarette smoking, genetic predisposition, exposure to airborne substances, socioeconomic status, airways reactivity, and allergies have been found to be important risk factors.
- New advances have been reported in **measuring the velocity of mucus transport** by the ciliated epithelium of the airways, in collecting normal mucus for physiochemical analyses, and in measuring transtracheal water and ion variations. These will all permit future study of the role of pulmonary secretions in chronic obstructive lung disease.

Advances in science proceed by an infinite number of small steps, each building on past achievements. In the last five years, many such small steps have been taken. Progress has been notable particularly in the areas of detection of early lung abnormalities in patients with emphysema and chronic bronchitis, in the identification of well individuals who may be at high risk of developing these diseases, in a broader concept of the role of proteases and antiproteases in the pathogenesis of lung disease, and in understanding the importance of cigarette smoking cessation.

State of the Science in 1977

In 1972, a patient with emphysema or chronic bronchitis had little chance of recovery from either disease because by the time the patient consulted a physician, the disease had progressed irreversibly. The importance of a means of detecting the disease early enough for meaningful therapeutic intervention was considered a matter of great urgency.

As a result of program initiatives taken in the past five years, simple screening tests for pulmonary function have now been developed that can be used to diagnose pulmonary emphysema in its subclinical stages—an important advance. A second development—a radiographic technique—makes possible the direct visualization of early alterations associated with airways obstruction.

In 1972, cigarette smoking was singled out as the primary risk factor in emphysema and chronic bronchitis. Since then, a number of additional risk factors have been identified: genetic predisposition, exposure to airborne substances, socioeconomic status, airways reactivity, and allergies. A new concept is developing that places emphasis on the interaction of all of these risk factors.

Cessation of the smoking habit has been found to restore the lung to a rate of aging and loss of function paralleling that of non-smokers, halting the steeper decline in function characteristic of smokers' lungs. In the past five years, an increased public education effort has been made to reduce cigarette consumption and to acquaint the public with the growing evidence of the harmful effects of smoking.

Chemical extracts of cigarette smoke (described in the section on Structure and Function of the Lung) have been shown to affect adversely the ability of macrophages to clear bacteria and debris from the lung. These harmful substances also injure leukocytes (white blood cells) that contain at least three proteases—elastase, cathepsin G, and collagenase. Thus, smoking is believed to trigger the unloading of proteases that cause connective tissue damage and eventually lead to emphysema and chronic bronchitis.

Recent research findings have led to a deeper appreciation of the important role of proteases and antiproteases in the pathogenesis of lung disease, especially those, like emphysema, that involve alveolar connective tissue damage and airspace enlargement. To check destruction of the elastin fibers in the alveolar walls, a delicate, controlled interaction of proteases and antiproteases is vital. Many biochemical variants of antiproteases have recently been identified, some of which fail to be released by the liver and thus are absent from blood plasma. The result is an imbalance between proteases and antiproteases, with resulting tissue destruction. New studies are being carried out to identify, isolate, and purify these antiproteases and to learn more about their mechanism of action, their genetic control, and their release from the liver.

As planned, a controlled clinical trial is under way to evaluate the efficacy of nocturnal low-flow oxygen therapy in comparison with continuous

therapy. The effects on morbidity will be assessed by measuring a number of parameters such as exercise tolerance, red cell mass, neuropsychologic functions, and socioeconomic cost.

These important advances place us at the point where we can anticipate future benefits for emphysema and chronic bronchitis patients, although these diseases continue to pose serious health problems to the nation. But with new tools for diagnosis and improved therapy, there is every reason to believe that progress will be made as future research efforts go forward and as the results of the current program are translated into more adequate prevention, detection, and control.

Program Goals: 1978–1982

Directed toward the ultimate goal of prevention and control of chronic obstructive lung diseases, the Institute's program seeks to find means to delay or reverse disease progression through greater knowledge of pathogenesis; and to ameliorate the morbidity and mortality due to these diseases through improved techniques for early diagnosis and more effective management.

Specific goals to be achieved during the next five-year period are:

- Characterize presymptomatic stages of chronic obstructive lung diseases and determine if such changes are reversible.
- Identify and better determine the relative contribution of risk factors such as cigarette smoking and environmental, socioeconomic, genetic, and other host factors to the incidence and exacerbation of chronic bronchitis and emphysema.
- Determine the role of proteases in the development of pulmonary emphysema, and assess the role of protease inhibitors in preventing lung tissue damage.
- Reduce the frequency and morbidity of asthma through characterization of disease etiologic and pathogenic processes.
- Evaluate current therapeutic regimens for chronic obstructive lung disease in terms of their efficacy, cost, and indications, and develop new therapeutic interventions based on an improved understanding of pathophysiology.

Research Activities: 1978–1982

Capitalizing on the momentum achieved to date in progress toward prevention and control of chronic obstructive lung disease, research activities over the next five-year period will principally carry forward ongoing projects.

Continuing research efforts include:

- Longitudinal studies of the natural history of chronic bronchitis and emphysema, emphasizing when in the course of the disease deleterious changes can be arrested or reversed through therapeutic interventions.
- Investigations of pulmonary function tests that detect presymptomatic stages of chronic obstructive lung disease.
- Investigations of pulmonary function in individuals identified as heterozygous for alpha-1-antitrypsin deficiency.
- Efforts to foster use of standardized procedures—pulmonary function tests, respiratory symptom questionnaires, and chest x-rays—in longitudinal and other population studies of chronic obstructive lung disease.
- Studies to correlate biochemical and physiologic alterations in early stages of chronic obstructive lung disease.
- Characterization of the mediators involved in asthma.
- Studies of the efficacy of nocturnal oxygen therapy in chronic obstructive lung disease.
- Studies on the use of intermittent positive pressure breathing for treatment of chronic obstructive lung disease.

Studies to be implemented:

- Programs to determine changes in pulmonary function in individuals participating in smoking cessation programs.
- Assessment of possible adverse effects on pulmonary function of aversive techniques (e.g., "rapid smoking") used to encourage cigarette smoking cessation.
- Studies to reduce frequency and morbidity

of asthma through characterization of the etiology and pathogenesis of the disease process.

- Evaluation of the relative efficacy and cost of various therapeutic and rehabilitative techniques to manage chronic obstructive lung disease.

Studies under consideration for increased support:

- Population studies to quantify the relative roles of various risk factors—cigarette smoking, environmental, socioeconomic, genetic, and other host factors—in the etiology of chronic obstructive lung disease.
- Role of proteases in development of pulmonary emphysema and the assessment of protease inhibitors in preventing lung tissue damage.

Schedule

Studies under consideration for increased support and research activities listed under continuing research activities (with the exception of investigations of pulmonary function in individuals identified as heterozygous for alpha-1-antitrypsin, studies of the efficacy of nocturnal oxygen therapy, and studies on the use of intermittent positive pressure breathing) are anticipated to continue through FY 82. These three studies will be completed before FY 82.

Studies to be implemented will probably be initiated in FY 79 or FY 80.

Pediatric Pulmonary Diseases

Hyaline membrane disease (neonatal respiratory distress syndrome), cystic fibrosis, and bronchiolitis are diseases of infancy or childhood that involve the lung and constitute major health problems in these age groups.

In hyaline membrane disease, the infants' lungs at birth are immature, especially with respect to the ability to synthesize adequate amounts of surfactant, a surface active material. The disease is restricted almost exclusively to infants born prematurely, has its onset at birth, and can result in either death or recovery within a few days, depending on whether or not prompt medical intervention is available. About 40,000 babies are born each year with hyaline membrane disease, and many of these die unless they are given prompt treatment.

Cystic fibrosis is a genetically determined disease, characterized by alteration in glandular body secretion. The dysfunction is generalized and affects sweat glands and pancreatic gland secretions. It is distinguished by excessive secretion of mucus, causing bronchial obstruction. The cause of death of cystic fibrosis patients is usually due to the pulmonary involvement. The gene-determined biochemical defect is not known, but the basic error of metabolism apparently affects sodium or other ions. Cystic fibrosis occurs in one of every 2,000 live births, and approximately 5 percent of the general population in the United States carries the gene for this disorder.

In bronchiolitis, there is chronic obstruction of the upper and lower respiratory tracts, usually seen in young infants at three to 15 months of age. The possibility exists that the condition may predispose affected children to adult chronic obstructive diseases, such as emphysema and chronic bronchitis, but this has not been unequivocally established.

State of the Science in 1972

Where did we stand with respect to these diseases in 1972? The cause of hyaline membrane disease of the newborn was unclear, although an immature lung and a lack of surfactant were implicated in its etiology. Cystic fibrosis was known to be caused by a genetic defect, but the pathogenesis of the disease was poorly understood, and the exact biochemical defect caused by the gene was unknown. The possible long-term effects of early childhood bronchiolitis on the development of more serious obstructive lung diseases in adulthood, such as emphysema and chronic bronchitis, were suspected but unproved. Clearly, an aggressive program to tackle these unanswered questions was needed.

Goals Through 1977

The following program goals were thus defined as important targets for future research efforts on

pediatric pulmonary diseases:

- Elucidation, through fundamental studies, of the biochemical changes associated with hyaline membrane disease, and development of methods to detect these changes prenatally so that therapy could be initiated at birth.
- Improved therapy for hyaline membrane disease by development of new devices and ways to initiate treatment as soon as possible, through emergency services for rapid transfer of infants to intensive care units.
- Determination of the basic biochemical defect caused by the gene for cystic fibrosis, making possible accurate methods for early detection and therapy.
- More information on the chemistry and pharmacology of mucus production in health and disease, on its elasticity and viscosity, and on the structural organization of water molecules in mucus.
- Initiation of epidemiologic studies to determine, prospectively, the long-term effects of bronchiolitis in childhood on the occurrence of chronic obstructive lung disease in adults.

Accomplishments Through 1977

Important breakthroughs have been reported as the result of programs developed in the last five years:

- It is now possible to **detect hyaline membrane disease before birth,** using the technique of amniocentesis. A sample of the amniotic fluid bathing the fetus is removed and analyzed for two lipids, lecithin and sphingomyelin, components of pulmonary surfactant. The ratio between the two components can be used as an index of fetal lung maturity. More recently, two lung-specific proteins have been identified in alveolar surfactants. Analyzing amniotic fluid for these two proteins allows for greater sensitivity and specificity in prenatal diagnosis of this disease. This important step toward early detection of hyaline membrane disease now makes possible the earliest possible care of the afflicted newborn.
- **An effective therapy for hyaline membrane disease** has resulted in a survival rate of up to 90 percent in some studies. The therapy is known as CPAP—continuous positive airway pressure. A pressure above atmospheric level is maintained at the airway opening throughout the respiratory cycle, keeping the lungs expanded and assuring an adequate supply of oxygen to the infant with immature lungs. Since 1973, increasingly favorable evidence has accumulated on the use of one particular technique—nasal prongs—for application of CPAP, and it has become a widely used, successful therapy.
- A promising step was taken toward **prevention of hyaline membrane disease** with the report of a lung growth-promoting factor isolated from human pregnancy urine.* When fetal lambs were infused with the growth factor and later delivered prematurely, their lungs were structurally more mature than those of the untreated controls and no hyaline membrane was seen in the experimental group.
- An observation, first reported from New Zealand, that **administering drugs** (for example, **corticosteroids**) to the mother shortly before parturition might prevent hyaline membrane disease is being followed up with a validation study initiated by the NHLBI. It has been found in a number of animal studies that corticosteroids administered to the mother do in fact increase the maturity of lung tissue of fetal animals. One controlled trial on human beings showed a similar result. However, before recommending widespread use of corticosteroids as a preventive treatment, careful evaluation of possible risks versus benefits must be carried out in a well-controlled clinical trial.
- **Elastin** in the mature lung has a different amino acid composition from that of the developing lung, and the mature form does not appear until the 32nd to 35th week of

* See also the section on structure and function of the lung.

fetal life. In infants dying of hyaline membrane disease, the amino acid composition of elastin has been found to correspond to that of a fetus 20 to 30 weeks of age.

- Great effort has been devoted to the **identification of unique substances,** i.e., biochemical markers of altered genetic makeup, **in patients with cystic fibrosis.** A ciliary inhibitory factor has been isolated and partly characterized from the tissue culture medium of cells taken from parents of cystic fibrosis patients. A similar factor has been found in serum, urine, and saliva from patients with cystic fibrosis. The finding that the factor seems to appear in parents with only one gene for the disorder, not two as the patients have, opens the possibility of genetic screening of well individuals to determine whether they are carriers of the gene for cystic fibrosis.
- **A second factor, or factors, isolated from saliva and serum of patients with cystic fibrosis,** inhibits transport of electrolytes across cell membranes. At present, it is not known whether these are different or the same as the factor that inhibits ciliary activity.
- **A new technique for photographing cells that secrete mucus** has been described. This is an important step toward understanding what goes wrong when mucus glands begin to oversecrete and clog the airways of patients with cystic fibrosis, as well as chronic bronchitis and asthma. The technique involves the use of powdered tantalum, an inert metal that is opaque to x-rays. When sprayed into the trachea of laboratory animals, the mucus glands can be viewed with a fiberoptic bronchoscope. Thus, any increases in mucus secretion or any change in mucus gland structure or function can be directly observed. For example, using this technique, researchers have observed that stimulation of parasympathetic nerves results in greater water flow into the airways and a stickier mucus secretion. This suggests that, in cystic fibrosis and other obstructive lung disorders, some abnormality in the system linking parasympathetic nerves with cellular functions might explain the excess mucus production.
- **Glycoproteins from the mucus** taken from trachea and bronchi of patients with cystic fibrosis have been compared with samples taken from control subjects. It appears that glycoproteins from the patients contain a predominance of a highly sulfated component.
- **Early detection of the effects of bronchiolitis in infants** is now possible through the development of a spirometer designed specifically for measuring lung function. In the past, progress in this area had been hampered by the difficulty in studying pulmonary function in children too young to cooperate.
- From records kept over the past 40 years, clinicians have noted that **patients with asthma frequently have a history of bronchiolitis during infancy.** Also, adults with obstructive pulmonary diseases such as emphysema and chronic bronchitis often date the onset of their problem as starting in infancy or early childhood.

State of the Science in 1977

In reviewing research accomplishments over the past five years, the most striking advances toward a solution to the problems posed by pediatric pulmonary diseases have been made in the prevention of hyaline membrane disease. Progress against this disease provides a satisfying model of a success story in disease control. This progress has developed stepwise along the research spectrum defining the Institute's overall strategy (Figure 2) and three phases are clearly identifiable: (1) acquisition of new knowledge through support of basic research, applied research and development, and clinical investigation; (2) validation studies—clinical trials based on these research findings; and (3) translation of this knowledge into improved health care services for the public.

As a result of basic research findings, clinical trials, and educational efforts directed to health care personnel, hyaline membrane disease can now be diagnosed before birth using amniocentesis. Prevention of hyaline membrane disease seems a realistic possibility for the future as the result of two research

leads: a factor, isolated from human pregnancy urine, which stimulates fetal lung maturation in lambs and prevents hyaline membrane disease in premature animals, and corticosteroids which, when administered to the mother shortly before parturition, appear to speed lung maturation of the fetus in animals and possibly in human beings as well.

In spite of these gains, however, important questions regarding etiology, pathogenesis, and long-term effects of the disease on the neurological and pulmonary development of the child remain unanswered. Many of the studies needed are either impractical or unethical to conduct on human neonates. For this reason, a recently developed primate model is being followed with great interest and expectation.

One of the most important developments in cystic fibrosis is improved pulmonary care, with the result that most patients today are surviving to adulthood, often to the third decade of life. This means that cystic fibrosis is no longer exclusively a pediatric disease, and pulmonary physicians will be seeing increasing numbers of adult cystic fibrosis patients in the future. Mindful of this, the Institute recently sponsored a workshop so pulmonary experts could exchange ideas on the best medical care approaches to these patients and also on future research needs.

Concerted efforts to identify the biochemical lesion in cystic fibrosis have begun to yield results. Unique factors have been identified in the body fluids of cystic fibrosis patients, and even in their parents who, though free of the disease, are carriers of the gene. The factors inhibit ciliary action and also electrolyte transport across cell membranes. Undoubtedly, these leads will be actively pursued in future research efforts.

Another important research focus in cystic fibrosis has been on mucus—its composition and its secretion—to learn more about why mucus is overproduced in cystic fibrosis, as well as in other obstructive lung diseases, such as chronic bronchitis and asthma. A newly developed technique using tantalum and fiberoptic bronchoscopes allows direct visualization of mucus-secreting cells in animals and promises to open the way to a new understanding of mucus secretion in both healthy and diseased states. Since excess mucus production is the cause of the severe bronchial complications in cystic fibrosis and other chronic obstructive diseases, this area is of great importance for future understanding of abnormalities in mucus secretion control in the tracheobronchial tree.

In bronchiolitis, a pulmonary function test technique, the spirometer, has been redesigned specifically to study infants; this should improve greatly our ability to study this condition.

Thus, we see tangible progress against pediatric pulmonary diseases. Gaps in our knowledge are slowly closing. Since 1972, substantial steps have been taken toward a greater understanding of hyaline membrane disease, cystic fibrosis, and bronchiolitis, although it is clear that much more needs to be done. But as future program efforts are focused on research needs, significant steps will no doubt be taken toward greater prevention and control of pediatric pulmonary diseases.

Program Goals: 1978–1982

Working toward the prevention of pediatric pulmonary diseases through increased knowledge of the underlying disease process, the Institute plans to achieve the following specific goals during the next five-year period.

Hyaline Membrane Disease:

- Determine maternal, developmental, and environmental factors that increase risk of hyaline membrane disease.
- Characterize the clinical, pathological, physiologic, biochemical, and molecular events associated with the onset and cause of the disease syndrome.
- Determine if subsequent development is impaired in children who recover from hyaline membrane disease.

Cystic Fibrosis:

- Identify cystic fibrosis factors in patients, and genetic markers in heterozygous carriers of the cystic fibrosis gene.
- Elucidate normal mechanisms involved in mucociliary clearance, and determine how these are modified in cystic fibrosis.
- Develop therapies and procedures for man-

agement of patients with cystic fibrosis.

Bronchiolitis:

- Characterize the pathologic, immunologic, and physiologic manifestations associated with the onset and course of bronchiolitis.
- Evaluate the role of bronchiolitis in subsequent disorders of the airways and lung parenchyma.
- Assess the role of genetic, immunologic, developmental, and socioeconomic factors that may be related to the occurrence and severity of bronchiolitis.

Research Activities: 1978–1982

Hyaline Membrane Disease

Prenatal assessment of lung maturity by analysis of the amniotic fluid now makes feasible the earliest possible care of newborns with hyaline membrane disease. Further research, as indicated below, is needed to advance both prevention and treatment.

Continuing research efforts include:

- Investigations to characterize the clinical, pathologic, physiologic, biochemical, and molecular events associated with normal lung development, and the onset and course of hyaline membrane disease.
- Trials of the efficacy of antenatal administration of steroids in prevention of hyaline membrane disease.

Studies under consideration for increased support:

- Investigations of maternal, developmental, and environmental factors that increase risk of hyaline membrane disease.
- Research to determine if subsequent development is impaired in children who recover from hyaline membrane disease.

Cystic Fibrosis

Continuing research efforts include:

- Studies to identify cystic fibrosis factors in patients, and genetic markers in heterozygous carriers of the cystic fibrosis gene.
- Studies to identify pulmonary cells or tissue sites damaged or altered during the various stages of cystic fibrosis with emphasis on the earliest detectable structural changes in lung tissue.

Studies under consideration for increased support:

- Investigations to elucidate normal mechanisms of mucociliary clearance and to determine how these mechanisms are modified in cystic fibrosis.

Bronchiolitis

Studies to be implemented:

- Research to characterize the pathologic, immunologic, and physiologic manifestations associated with the clinical onset and the course of bronchiolitis.
- Investigations of the role of genetic, immunologic, developmental, and socioeconomic factors relevant to the occurrence and severity of bronchiolitis.

Studies under consideration for increased support:

- Research to evaluate the role of bronchiolitis in subsequent disorders of the airways and lung parenchyma.

Schedule

Hyaline Membrane Disease

The continuing research activity to characterize events associated with normal lung development and the onset and course of hyaline membrane disease will continue through FY 82. Trials of the efficacy of antenatal administration of steroids will be completed before the end of FY 82. Research activities listed as studies under consideration for increased support will continue through FY 82.

Cystic Fibrosis

All research activities listed above will be completed by FY 82. In addition, as resources permit, the NHLBI will support in FY 79 or FY 80 initiatives recommended by the ongoing Task Force on Cystic Fibrosis.

Bronchiolitis

Studies to characterize the pathologic, immu-

nologic, and physiologic manifestations associated with the clinical onset of bronchiolitis and studies to assess the role of genetic, immunologic, developmental, and socioeconomic factors relevant to the occurrence of bronchiolitis will be initiated in FY 79 or FY 80.

Studies to evaluate the role of bronchiolitis in subsequent disorders will continue through FY 82.

Fibrotic and Immunologic Lung Diseases

Exposure to a large number of toxic airborne agents can set off allergic or immunologic responses leading to pulmonary injury and a number of fibrotic and immunologic lung diseases, such as asthma, pulmonary fibrosis, hypersensitivity pneumonitis (pigeon breeder's or farmer's lung), and noninfectious granulomatosis.

Asthma is an immunologic disease of major importance. It is the most common chronic pulmonary disease, affecting millions of Americans. It can begin in early childhood and often can last a lifetime. Asthma is a disease characterized by increased responsiveness of the bronchi to various stimuli. Constriction of the airways results, trapping the irritants that precipitate the allergic response and causing congestion of the airways and difficulty in breathing. Excess mucus production is characteristic.

Among fibrotic diseases are idiopathic fibrosis, hypersensitivity pneumonitis, and noninfectious granulomatosis. The etiology of idiopathic fibrosis is unknown, but in the case of the other diseases, exposure to irritants sets off immunologic or fibrotic responses. In fibrotic diseases, there is reduced ventilatory capacity, abnormal gaseous exchange, and appearance of inflammatory cells—lymphocytes, macrophages, and plasma cells—in the lungs of patients with these diseases.

The offending environmental agents include viruses, bacteria, and radiation; exposure to substances such as molds, dust, pollen, silica, and asbestos; and pollutant gases such as nitrogen dioxide, ozone, and sulfur dioxide.

Fifteen to 20 percent of noninfectious disorders of the lung are due to fibrotic lung disease. Although there are many separable disease entities, all share the abnormal physiologic response and the presence of inflammatory cells.

Most of these diseases can be prevented if the irritants are removed from the environment. For this reason, an important goal in the control of fibrotic and immunologic lung diseases is the dissemination of information about the causes of these diseases and how to avoid them.

State of the Science in 1972

Although it was appreciated in 1972 that many external agents could elicit immunologic or fibrotic responses in the host, very little was understood about the nature of the antigens, the immune injury that followed, or the mechanisms that trigger the abnormal response. Advances in biochemistry, immunology, and pharmacology had not been brought to bear on these diseases. It was suspected that collagen synthesis in the lung was altered in fibrotic disorders, but studies were needed on the mechanisms of collagen synthesis and degradation to pinpoint specifically what biochemical abnormalities might be present. Only in this way could therapy be developed and targeted to the specific metabolic peculiarities accompanying these diseases.

Goals Through 1977

The major obstacle to progress toward improved therapy and management of patients with fibrotic and immunologic lung diseases was clearly the lack of fundamental information about the hypersensitivity response. What was needed was a multidisciplinary collaborative approach among immunologists, biochemists, and physiologists with pulmonary physicians who had direct contact with patients and who knew what basic information was lacking.

Consequently, in late 1972, the NHLBI singled out key areas as most urgently needing study and identified the following goals:

- To obtain more information about the synthesis and degradation of collagen and the immunologic response and defense mechanisms of the lung.
- To develop pharmacologic agents capable of inhibiting alterations in connective tissue metabolism that lead to pulmonary fibrosis,

and ways to stimulate defense mechanisms against immunologic lung diseases.

- To investigate etiologic factors in population groups characterized by unusual prevalence of fibrotic and immunologic lung disease.

Accomplishments Through 1977

No dramatic breakthroughs have been made in the past five years in our ability to control or prevent fibrotic and immunologic diseases of the lung. No new pharmacologic agents have been discovered. We still lack basic information about why patients with these diseases are hypersensitive to environmental stimuli and about why fibrosis occurs, and we are ignorant of ways to counteract these responses. Nevertheless, important new information is at hand from research on these problems. Following are some research findings that serve as signposts for future research efforts:

- Significant advances have been made in the **early detection of asthma** through inhalation challenge techniques. These tests, which can identify individuals with asthma before it is clinically apparent or advanced, involve challenging an individual with compounds known to cause bronchial or immunologic responses. Traditionally, nonspecific compounds such as methacholine were used as testing agents, but now specific substances (antigens) are used as the challenge material. Responses to these antigens can lead to a better understanding of precise disease mechanisms.
- **Lymphocytes** (a type of white blood cell) from **asthmatics** contain lower levels of a key biochemical substance, cyclic adenylate monophosphate, than those from normal subjects. This deficiency points to possible biochemical abnormalities in the cell membranes of asthmatics.
- Clarification of **role of collagen in fibrotic lung diseases** has come from studies of material obtained from human lung biopsies. The average density of lung collagen, the rates of collagen synthesis per cell, and the percentage of collagen synthesis were all found to be normal. Thus, what appears to be an excess of connective tissue in fibrotic diseases may actually be due to local changes in lung structure which result in severe physiological abnormalities, not to changes in the average collagen density in the lung.
- **Type I collagen,** one of the forms of collagen found in normal lungs, has been recently found to be antigenic in individuals with pulmonary fibrosis. In a laboratory test, peripheral blood lymphocytes from more than 95 percent of patients with pulmonary fibrosis recognized collagen as antigenic, as compared with zero percent in normal subjects. This observation may lead to a technique for early diagnosis of pulmonary fibrosis.
- **Promising animal models** such as hamsters, rabbits, guinea pigs, and baboons have been described for pulmonary fibrosis and hypersensitivity pneumonitis. Using specific antigens and other challenges, lung responses that resemble closely the lesions of human beings with these diseases have been elicited from the animal models. This research promises a deeper understanding of the pathogenesis of these disorders.
- **Sarcoidosis,** a symptomatic granulomatous disease, is found four times more frequently in individuals who carry two specific HLA antigens than in those who lack them. The antigens are formed under genetic control, suggesting possible familial predisposition to the disease. Also, the serum of patients with sarcoidosis was found to contain increased levels of the angiotensin-converting enzyme.* Thus, the presence of this enzyme and of HLA antigens may be used in the future as identifiers of high-risk groups in the population.

State of the Science in 1977

It is only in the past five years that immunologists, biochemists, pharmacologists, and pulmonary physicians have been encouraged to join together in a multidisciplinary approach to problems posed by

* See section on structure and function of the lung.

fibrotic and immunologic diseases. Since 1972, as the result of NHLBI program efforts, progress has been made toward a greater understanding of the hypersensitivity responses in these diseases. But we are not yet at the stage where new pharmacological agents or other therapies can be designed. Nor do we understand what causes the abnormal physiological response in patients with fibrotic diseases. We have no real clues as to abnormalities in collagen found in patients as compared with collagen from normal subjects.

A number of animal models have been developed that will permit us to follow more closely the sequence of events leading to lung disease when offending agents are present in the environment. Several specific antigens have been isolated that cause diseases such as asthma, pulmonary fibrosis, and hypersensitivity pneumonitis in animal models and in human beings. This, too, will permit progress toward more meaningful studies of etiology and pathogenesis.

Early detection of asthma, sarcoidosis, and pulmonary fibrosis may now become possible as the result of new tests. The possibility thus exists for identifying high-risk groups for these diseases.

In 1972, the central problem for better control and management of fibrotic and immunologic diseases was to understand more about the hypersensitivity responses of patients to external irritants. While some gains have been made, this problem remains and continues to be a focus of the Institute's research program. Scientists also need to develop new methods for defining the populations at risk of developing these diseases, and new drugs or other therapies to halt or to suppress immune reactions to damaging airborne agents. In the meantime, it is fortunate that most of these diseases can be prevented by avoiding exposure to injurious environmental agents.

Program Goals: 1978–1982

The overall goals of the Institute in this category of lung diseases are to prevent fibrotic and immunologic lung diseases through better understanding of specific airborne hazards and of the mechanisms by which they induce lung injury, and to improve early detection and clinical management of pulmonary fibrosis due to primary or secondary lung tissue injury.

Specific goals during the next five years are as follows:

- Identify specific agents responsible for fibrotic lung diseases and hypersensitivity pneumonitis, and establish dose-to-effect relationships between these agents and resultant lung reactions.
- Determine prevalence of fibrotic lung diseases and hypersensitivity pneumonitis, and characterize their natural history.
- Characterize biochemical, cellular, and immunologic events associated with the clinical onset and course of fibrotic lung diseases and hypersensitivity pneumonitis.
- Reduce frequency of occurrence and develop treatments for primary pulmonary fibrosis and for fibrotic reactions secondary to immunologic lung disease.
- Determine how the autonomic nervous system affects airway caliber of different levels of the bronchial tree in health and disease.
- Determine the role of epithelial damage in the sensitivity of bronchi on exposure to various respiratory irritants and establish the anatomical basis of the abnormalities.
- Determine functions of kinins, their release mechanisms and influence on airway smooth muscle.

Research Activities: 1978–1982

During recent years, the Institute has encouraged a multidisciplinary approach to etiologic, diagnostic, and therapeutic problems posed by fibrotic and immunologic lung diseases. Though much valuable information has been gained, among the vital facts still eluding investigators is what causes the abnormal accumulation of fibrous collagen-containing material in the lungs of patients with these diseases. Hopefully, pursuit of the following research activities will bring us these and additional answers during the next five years.

Continuing research efforts include:

- Investigations of specific agents responsible

for fibrotic lung diseases in occupational environments, with specific attention to dose-response relationships.

- Investigations of specific agents responsible for hypersensitivity pneumonitis in working and home environments, with special emphasis on measures to reduce or eliminate exposures.
- Epidemiologic studies of populations exposed to occupational hazards to the lung to elucidate the natural history of fibrotic lung diseases.
- Epidemiologic studies of populations exposed to organic dusts that cause hypersensitivity pneumonitis to elucidate the natural history of the disease.
- Development of animal models of fibrotic lung diseases and hypersensitivity pneumonitis.
- Investigations relative to the immunologic and biochemical responses to organic and inorganic dusts that lead to fibrotic lung diseases and hypersensitivity pneumonitis.
- Investigations of the role of the kallikrein-kinin system in the immediate hypersensitivity reaction of asthma.
- Studies of the functional relationship between the autonomic nervous system and airway resistance in the normal and diseased lung.

Studies to be implemented:

- Population studies to determine the relative contributions of occupational and nonoccupational factors in the occurrence of fibrotic lung diseases.
- Studies resulting in the early recognition and prompt treatment of the pulmonary manifestations of systemic diseases.
- Investigations to increase understanding of agents involved in drug-induced pulmonary disease and to increase recognition of early symptoms.
- Research on the mechanisms by which beta-sympathomimetic agents produce relaxation of bronchial smooth muscle.
- Investigations of the role of epithelial damage in the sensitivity of bronchi upon exposure to various respiratory irritants.

Studies under consideration for increased support:

- Investigations on the role of collagen in the development of pulmonary fibrosis.

Schedule

All studies listed under continuing research, except development of animal models, will continue through FY 82. Development of animal models, population studies to determine the relative contributions of occupational and nonoccupational factors in the occurrence of fibrotic lung diseases, and investigations of the role of collagen in the development of pulmonary fibrosis are anticipated to be completed before FY 82.

Studies resulting in the early recognition and prompt treatment of the pulmonary manifestations of system diseases and investigations to increase understanding of the agents involved in drug-induced pulmonary diseases are expected to begin in FY 79 or FY 80.

Respiratory Failure

Respiratory failure can occur in persons with many different acute or chronic conditions, such as postoperative or other trauma, fat embolism, drowning, drug overdose, sepsis, pneumonia, or late stages of diseases such as emphysema or chronic bronchitis. Healthy adults as well as those with previous pulmonary impairments can be affected in significant numbers. Acute respiratory failure affects approximately 200,000 adults each year.

In respiratory failure, the alveolar (air sac) ventilation is insufficient to provide adequate gaseous exchange. This results in dangerously low oxygen levels in the blood despite the presence of normal amounts of oxygen in the inhaled air. Fortunately, if recognized early and treated promptly, the condition is potentially reversible.

State of the Science in 1972

In 1972, sophisticated therapy was available for

treatment of patients with respiratory failure, but the technology was used primarily by experienced professionals and was not in widespread use. A great need was recognized for developing new modes of therapy that would be less costly, less complicated to administer, and more readily available to the medical and health professions. There was need for a critical evaluation of devices and techniques in use at that time and for improved diagnostic, monitoring, and rehabilitation methods.

Goals Through 1977

To deal with the problems of respiratory failure, the following goals were established in late 1972:

- To expand the research program on respiratory failure to ensure improvements in available devices and the development of new ones.
- To develop devices and techniques for efficiently monitoring the respiratory function of patients with impaired lungs.
- To develop improved invasive and noninvasive instruments for blood and respiratory gas analysis in patients with lung disease.
- To disseminate information to the medical profession and to health care personnel to keep them informed of the latest techniques for detection and therapy.

Accomplishments Through 1977

As a result of programs initiated by the Institute to achieve these goals, the following major advances have been made in improvement of therapeutic approaches to life support of the critically ill:

- **Moment-to-moment monitoring of blood gases** over prolonged periods is now possible in a clinical setting as the result of major improvements in blood gas measurement. New sensors that are accurate, stable, and rapid now permit the continuous monitoring of oxygen and carbon dioxide levels in acutely ill patients. This technique permits continuous evaluation of various therapeutic interventions.
- **Extracorporeal membrane oxygenation (ECMO)** for the treatment of patients suffering from acute respiratory failure has been the subject of a collaborative clinical trial begun in 1973. Under the conditions of the procedure, the results indicate that this procedure is largely ineffective. There was no difference in mortality rates in patients receiving ECMO in addition to conventional therapy as compared to control patients receiving only conventional therapy. This study is of value in discouraging both manufacturers from producing the oxygenators and physicians from using this expensive and largely ineffective therapy.
- Paralleling this clinical evaluation program, a **pathology center** was set up in 1975 to **compare the effects of both extracorporeal membrane oxygenation and conventional treatments.** If patients succumb to respiratory failure, tissues are obtained for study, and evidence is sought of beneficial or detrimental effects of therapy. Tissues are examined by light and electron microscopy for various biochemical and histochemical properties. Definitive results from this program are not yet available.
- In 1971, a program was initiated to study the **mechanisms by which oxygen therapy might cause lung damage** and to identify methods of detecting oxygen toxicity prior to the occurrence of irreversible symptoms. The dangers of prolonged use of high concentrations of oxygen had long been suspected. Using animals, the study revealed that abnormalities such as tracheobronchitis, marked depression of mucus clearance, and damage to specific lung cell types take place in the respiratory tract within days of continuous high concentrations of inhaled oxygen (higher than 75 percent). When high concentrations of oxygen were administered over a period of months to the experimental animals, proliferated and engorged pulmonary capillaries were found with oxygen levels as low as 35 to 40 percent. These findings in animals point to a reassessment of long-term clinical use of

high, or even moderately high, concentrations of oxygen, and serve as a warning to physicians and health service personnel.

- A **small diaphragm pacemaker** can be implanted beneath the skin of the chest wall for pacing breathing in seriously ill patients. Several patients were found to be symptom-free for at least six months following implantation of these devices.

State of the Science in 1977

Over the past five years, program emphasis has been on improving life-support devices for critically ill patients suffering from respiratory failure. We are definitely further along toward improved and wider use of this therapy than we were in 1972. Noteworthy progress has been made in the perfection of blood gas sensor devices for monitoring oxygen and carbon dioxide levels in acutely ill patients, permitting continuous evaluation of various therapeutic interventions. Advances have also been made in determining continuous distributions of ventilation-perfusion ratios (the ratio of ventilation to blood flow). Since ventilation-perfusion ratios are not uniform throughout the lung, the new technique is potentially valuable in detecting subtle signs of disease, not previously possible.

Artificial lungs and breathing pacemakers have been designed and are being tested in a number of clinical centers for their short- and long-term effects. The extracorporeal membrane oxygenator (ECMO) has been found to be largely ineffective as a therapy for patients with acute respiratory failure. Such negative results are important in deterring both manufacturers from producing such expensive equipment and physicians from adopting their use.

In spite of this real progress, however, what is lacking now is a precise understanding of the lung's repair mechanisms and of the biochemical and physiological responses of the lung to injuries sustained in acute respiratory failure. Without this basic information, efforts to develop improved techniques and better methods for early detection, treatment, and management will be impeded. A union of effort is needed between basic research scientists—biochemists, hematologists, microscopists, physiologists, cell biologists—and clinicians, in a multidisciplinary attack on the fundamental aspects of respiratory failure, an important and largely unexplored area of research.

Program Goals: 1978–1982

To reduce death and disability from respiratory failure, the Institute's overall goal is to improve the diagnosis and management of acute respiratory failure in the adult through better understanding of the structural, biochemical, and physiologic mechanisms of acute lung injury. Specific goals directing the Institute's program during the next five years are as follows:

- Characterize the mechanisms involved in lung injury, and identify precipitating factors that result in acute respiratory failure.
- Determine how lung tissue changes associated with acute respiratory failure can be arrested or reversed.
- Develop noninvasive techniques for early detection and continuous monitoring of acute respiratory failure.
- Assess the efficacy of current modes of therapy for acute respiratory failure in the adult, and develop more effective supportive and curative procedures.

Research Activities: 1978–1982

Research in respiratory failure is now emphasizing disease control as a result of increased knowledge of the fundamental mechanisms of pulmonary injury, etiology and the pathogenesis of disease. The Institute's program over the next five years is as follows:

Continuing research efforts include:

- Development of noninvasive techniques for early detection and continuous monitoring of acute respiratory failure.

Studies to be implemented:

- Through Specialized Centers of Research (SCORs), initiation of interdisciplinary approaches to elucidate mechanisms involved in lung injury; identification of precipitating factors that result in acute respiratory failure; determination of how degenerative changes

can be arrested or reversed; and improvements in the detection and clinical management of acute respiratory failure in the adult.

Schedule

It is anticipated that research activities listed under continuing research and studies under consideration for increased support will be completed before the end of FY 82.

The studies to be developed at the SCORs will be initiated in FY 78 and completed by the end of FY 82.

Pulmonary Vascular Diseases

Three abnormal conditions are included in pulmonary vascular diseases: cor pulmonale, pulmonary hypertension, and pulmonary edema. Precise data on their contributions to morbidity and mortality, or on their incidence and prevalence, are not available owing to lack of dependable methods for early and precise diagnosis.

In cor pulmonale, the right ventricle of the heart, which pumps blood to the lungs, becomes greatly enlarged as a result of diseases affecting either the structure or the function of the lung. There is a chronic increase in the work load on the right ventricle resulting in its enlargement, and ultimately, its failure.

Pulmonary hypertension is characterized by the elevation of pulmonary arterial pressure to levels markedly above what is accepted as normal. In the absence of cardiac or pulmonary disease, elevation of pulmonary arterial pressure can also be caused by high altitude, or by ingesting certain drugs and chemicals. Autopsy studies indicate that pulmonary hypertension is much more common than was previously thought.

In pulmonary edema, there is an abnormal accumulation of fluid in the lung, outside the vascular system. Unless detected early in its clinical course, prompt and meaningful therapy is difficult.

State of the Science in 1972

In 1972, it was recognized that the most pressing problem affecting all three of these pulmonary vascular diseases was our inability to detect them in time to help the patient. The diagnosis for pulmonary hypertension at that time was made by right heart catheterization, obviously not a practical method for screening early cases. Noninvasive diagnostic techniques were badly needed. In pulmonary edema, there was no method that could detect the condition while the patient was still clinically asymptomatic. It was imperative that research efforts be made to correct these gaps in our knowledge and in our ability to diagnose and treat vascular disorders of the lung.

Goals Through 1977

The following major program goal was set in 1972:

- To stimulate the development of noninvasive, safe, and reliable techniques for early detection of cor pulmonale, pulmonary hypertension, and pulmonary edema.

Accomplishments Through 1977

The following significant steps toward achieving this program goal are:

- **Improved detection of pulmonary edema** is a future possibility with the development of a rapid and accurate method for measuring alterations in lung weight using a mass spectrometer coupled with a minicomputer. The procedure is still in its developmental stage and is not yet used routinely as a clinical procedure. The technique permits noninvasive measurement of patients in ventilators and those who are breathing spontaneously. The accuracy, portability, and speed of this device make it a promising diagnostic procedure.
- New approaches toward the **noninvasive measurement of pulmonary vascular pressure** are being evaluated. Three such techniques under study are: (1) echocardiography, where the motion of the pulmonic valve between the pulmonary artery and the heart is used to calculate artery pressure; (2) bubble ultrasonic resonance pressure, where the resonance frequency from stable gas bubbles is

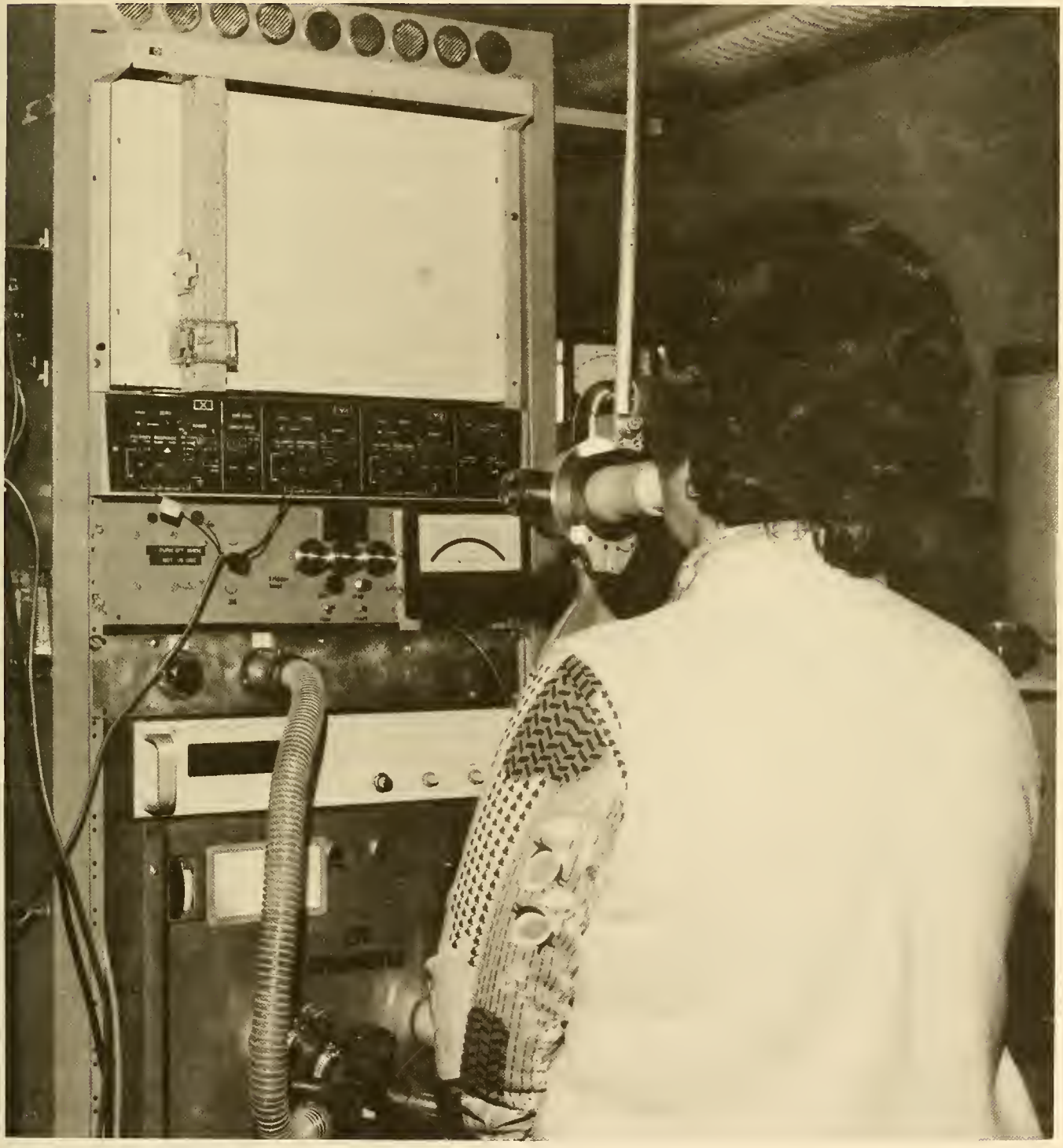
measured as the bubbles flow through the pulmonary artery. (The resonance frequency is dependent on the surrounding blood pressure); and (3) Doppler flow techniques to determine blood flow, pulse wave velocity, and changes in diameter of the pulmonary artery. From measurements such as these, pulmonary artery pressure can be calculated.

- Unquestionably, a most significant research finding (described also in the section on Structure and Function of the Lung) has been the identification of the endothelial lining of pulmonary capillaries as the **major site for the transformation of angiotensin I to angiotensin II,** a potent hypertensive substance. This has given birth to a new concept of lung function: the lung as an endocrine organ. Recent evidence suggests that other physiologically important substances such as catecholamines and peptides can also be altered in endothelial cells. These observations have important consequences not only for the regulation of pulmonary blood pressure and other lung functions, but for the whole body, since all the blood from the right side of the heart passes to the lungs for oxygenation on its way to the rest of the body.
- An important recent discovery is the **purification of two hitherto unidentified hormonal substances from lung tissues.** The hormones are peptides, and like other peptide hormones such as insulin, they may prove to be important regulators of body function. The newly isolated lung peptides have potent and opposite actions on airways, blood vessels of the lung and systemic circulations, and other organ systems. One peptide relaxes airways and blood vessels while the other contracts them. Between the two, therefore, the lung has the potential for modifying or regulating some aspects of its own function as well as systemic blood flow and blood pressure. Furthermore, the peptide that elicits contraction of airways could be an important mediator of asthmatic reactions, while the relaxant peptide has potential usefulness as a bronchodilator, and thus may prove of value in the treatment of asthma. Research is going forward on synthesizing these hormones and developing antibodies to them.
- Basic research into the **regulation of the pulmonary circulation** and studies of the ultrastructural and biochemical aspects of vascular smooth muscle have been initiated. There are more than 10 known humoral substances that affect pulmonary artery pressure. For each of these, there are specific pharmacologic substances that can moderate their actions; examples include histamine and antihistamines, adrenaline and alpha- and beta-adrenergic blocking agents, prostaglandins, and aspirin. Investigators are now studying the role of each of these substances in the regulation of pulmonary artery pressure.
- The **appropriateness of digitalis therapy** in patients with chronic lung disease is being reevaluated in the light of evidence that this treatment for heart disease may have adverse effects in a patient who also has lung disease. Digoxin, the active ingredient in digitalis, increases the sensitivity and contractility of pulmonary vascular smooth muscle and elevates pulmonary arterial pressure during hypoxia (low oxygen). This in turn places a burden on the right ventricle, leading to an adverse effect on the heart.

State of the Science in 1977

An important achievement in 1977 was the emergence of the new evidence that pulmonary circulation might be a center for neurohumoral control, affecting not only the pulmonary circulation and the lungs, but capillaries as the site of important metabolic conversions. This evidence has reinforced the concept of the lung as an endocrine organ. The important discovery of two peptide hormones in the lung undoubtedly will stimulate new program emphasis on basic research in this area.

The development of noninvasive methods for detecting pulmonary hypertension and pulmonary edema has been achieved. While these techniques are not yet in clinical use routinely, they hold great promise as effective noninvasive diagnostic proce-



Pulmonary function studies can sometimes give an early indication of lung disorders before symptoms appear. The electronic spirometer is measuring a forced vital capacity, which is being recorded on an x-y recorder.

dures that are accurate and rapid.

More basic research is needed on how pulmonary circulation is regulated since we know of at least 10 hormone-like agents that affect pulmonary artery pressure, and pharmacologic agents that can moderate their actions. Greater understanding of fluid and electrolyte transport across endothelial barriers as well as of lung lymph flow is also needed to elucidate the origin of pulmonary edema.

Since 1972, steps have been taken to find early detection methods for pulmonary vascular disease. Now that improved diagnostic techniques have been developed, more effective therapy becomes possible. And as fundamental investigations of normal and abnormal pulmonary circulation go forward with new emphasis on the ability of the lungs to transform drugs and hormones, we can anticipate future progress in our understanding and eventual control of pulmonary vascular disease.

Program Goals: 1978–1982

In pulmonary vascular diseases, early detection of disease is the key to effective patient management as increased fundamental knowledge of pulmonary circulation is to effective disease prevention. The overall goals of the Institute with respect to these diseases are to elucidate mechanisms underlying development of pulmonary edema, pulmonary hypertension, and cor pulmonale, and to bring this knowledge to bear on improving the diagnosis and treatment of these disorders.

Specific goals for the next five years are as follows:

- Characterize the dynamics of fluid and solute exchange, and the role of vasoactive mediators in the pathogenesis of pulmonary edema.
- Determine the structural, biochemical, and physiologic characteristics of pulmonary vascular smooth muscle, and the roles of hypoxia and vasoactive mediators in the etiology of pulmonary hypertension.
- Develop noninvasive techniques for early diagnosis and continuous monitoring of pulmonary hypertension and pulmonary edema.

Research Activities: 1978–1982

Recent Institute-sponsored research now makes possible the detection of early cases of pulmonary hypertension and pulmonary edema. Further work with this methodology will continue, but the principal emphasis of research activities during the next five years will be on the basic physiologic and pharmacologic parameters initiating disease and providing effective therapy.

Continuing research efforts include:

- Investigations of fluid and solute exchange in the normal and diseased lung, including assessment of the effect of vasoactive mediators on the integrity of the pulmonary endothelium.
- Development of animal models of pulmonary edema.
- Development of animal models of pulmonary hypertension and cor pulmonale.
- Development of noninvasive techniques for early detection and continuous monitoring of pulmonary hypertension and pulmonary edema.
- Investigation of the structural, biochemical, and physiologic characteristics of pulmonary vascular smooth muscle.

Studies under consideration for increased support:

- Role of hypoxia and vasoactive mediators in the development of pulmonary hypertension.

Schedule

Investigations of fluid and solute exchange, development of noninvasive techniques, and studies of the role of hypoxia and vasoactive mediators will continue through FY 82. All other research activities listed above will be completed before the end of FY 82.

BLOOD DISEASES AND BLOOD RESOURCES

By their very nature, problems of the blood affect every part of the body and are intimately related to cardiovascular and pulmonary diseases. Accordingly, the NHLBI conducts and supports a broad range of programs which have as their goals:

- Reduction of the morbidity and mortality resulting from diseases of the blood.
- Provision of adequate quantities of safe blood at reasonable cost to all who need them.

Progress toward these goals is achieved through research into the causes, prevention, diagnosis, and treatment of diseases of the blood, and studies and research on blood, the use of blood, and the management of the nation's blood resources.

This section examines the Institute's blood diseases and blood resources programs through four specific program areas: bleeding and clotting disorders; red blood cell disorders; sickle cell disease; and blood resources.

Bleeding and Clotting Disorders

Bleeding and clotting disorders represent two extremes of failure of the complex biological system by which the body maintains blood fluidity and simultaneously stops leaks from within the vascular system. These disorders impose a major demand on the nation's blood resources. In addition, they contribute to or cause a variety of diseases that, combined, represent a major cause of disability and death.

Excessive bleeding is a major cause of death or morbidity in various circumstances, such as after serious injury, after surgery, in hemophilia, and in cirrhosis of the liver. The threat of hemorrhage also limits the aggressive management of leukemia and other forms of cancer.

The consequences of clotting or thrombosis depend on the area of the body in which it occurs. In vessels of the heart, brain, lung, or other vital organs, even a very brief deprivation of blood supply can be catastrophic. Arterial thrombosis causes or complicates a variety of diseases in all parts of the body and can, for example, lead to such severe events as heart attack or stroke. Thrombosis in the veins can produce clot fragments that may be carried to the lung. This condition, pulmonary embolism, hospitalizes hundreds of thousands of persons and some estimates indicate that it kills as many as five times the National Center of Health Statistics' estimates of 10,000 individuals each year.

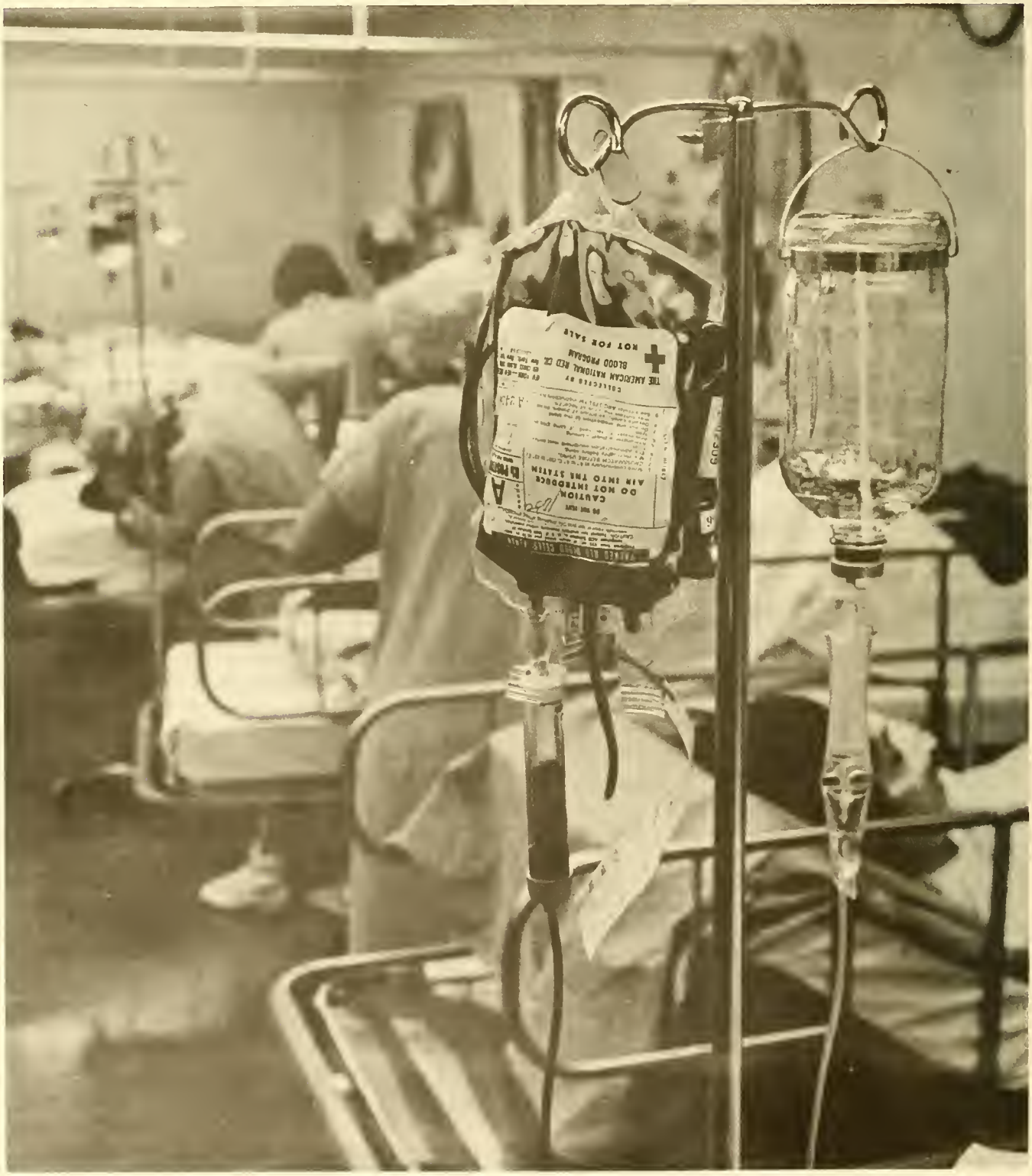
Bleeding and clotting in the small blood vessels and capillaries (microcirculation) contribute to or are primary mechanisms in many diseases: autoimmune disease, cancer, sickle cell anemia, drug toxicity, mismatched blood transfusions, and liver and kidney disease.

State of the Science in 1972

In 1972, we had only limited knowledge of the hemostatic system, and only preliminary knowledge at the molecular and cellular levels of the entities within it. Consequently, our ability to diagnose, treat, prevent, and cure was less developed than our appreciation of the vast consequences of these disorders.

Some types of excessive bleeding were known to result from an abnormality or deficiency, acquired or inherited, in certain of the elements of the hemostatic system. One group of bleeding disorders, the hemophilias, are a family of hereditary diseases. Although they affect a relatively small population of about 12,000, they constitute a major national health problem for two reasons: the required treatment is lifelong and costly (over $6,000 annually per patient), and treatment of the disease represents one of the largest single demands upon the nation's blood resources. Research advances in the previous two decades had identified two entirely different clotting proteins, Factors VIII and IX, and had determined that hemophilia resulted from a deficiency of either of these two factors. The capability to extract these factors from human blood donors existed but was expensive and inefficient.

The causes of both venous and arterial thrombosis were known to involve an interplay of the blood coagulation system, the platelets, the vessel lining, and the properties of flowing blood. It was recognized that a greater understanding of the role of thrombosis in myocardial and cerebral infarction, advances in early detection of thrombosis, and development of clot-preventing and clot-dissolving



Post-operative recovery room. An adequate blood supply is an essential component of many life-saving procedures.

drugs could offer significant health benefits to a large number of Americans. Since the mid-1960s, progress had been made in the understanding of the broad biological role of platelets, including involvement in microcirculation disorders, in the development of atherosclerosis, and in certain types of host-defense reactions. Yet, in 1972, details of platelet functions and how they could be manipulated to benefit the patient were inadequately understood.

Goals Through 1977

Recognizing the extensive health benefit potential to the American people of improved ability to prevent, diagnose, and treat bleeding and clotting disorders, the NHLBI launched a multifaceted program based on the following goals:

- To determine the biochemical nature and function of the elements involved in the coagulation process, and to investigate the possibility of manipulating them.
- To understand the interplay of the blood coagulation system, the platelets, the vessel lining, and the properties of flowing blood, as well as the role this interplay has in the development of thrombosis and atherosclerosis.
- To establish at least three Specialized Centers of Research to promote multidisciplinary research, clinical trials, and public and professional education to improve treatment and apply new approaches for cure and prevention of thrombosis.
- To develop improved techniques to harvest, concentrate, and store Factors VIII and IX so they could be made available, at a reasonable cost, to all hemophiliacs who need them.
- To develop programs to evaluate and compare noninvasive techniques to diagnose, measure, and monitor thromboembolic disorders.
- To clinically evaluate clot-preventing or clot-dissolving drugs in individuals at high risk from vaso-occlusive disease such as myocardial infarction and postoperative pulmonary embolism.

Accomplishments Through 1977

In the past five years, Institute initiatives directed toward these goals were responsible for remarkable advances in the basic knowledge of thrombosis and hemorrhage. This new knowledge base has greatly contributed to important advances in prevention, earlier detection, and improved therapy. Some of the results of these deliberate program efforts are:

- Major **advances in understanding key clotting and inhibiting factors:** prothrombin, vitamin K, and coumarin.
  - Outstanding among these has been the complete elucidation of the primary structure of prothrombin.
  - The biochemical action of vitamin K is becoming clear; vitamin K is essential for gamma carboxylation of the glutamic acid residues of prothrombin in the liver.
  - Coumarin is now known to be an inhibitor of the carboxylation step in the synthesis of prothrombin.
  - Prothrombin without gamma carboxyglutamic acid is inactive in the clotting process.

  These important discoveries not only add to our basic knowledge of the biochemistry of blood clotting, but also have clinical implications for anticoagulant drug development and therapy.
- One of the most interesting discoveries in the field of platelet function and, indeed, in clinical medicine has been the **elucidation of the role of aspirin** and how aspirin functions *in vivo*. It has been found that aspirin can inhibit clotting by blocking the action of the enzyme thrombokinase which catalyzes the formation of blood platelet clumping agents.
- Major advances have been made in **clinical management of hemophilia.** New procedures have been developed for isolating the Factor VIII molecule in a highly concentrated form. Dry concentrated Factor VIII preparations have been perfected, and home treatment is now possible and more widely accepted. Because home treatment allows for immediate

therapy for bleeding episodes, it can retard or prevent many of the complications of this disorder. The hemophiliac is also freed from the need for fresh whole blood or plasma transfusions and enjoys a freedom of activity heretofore unknown.

- NHLBI grantees have pioneered in developing an array of tests which, together, constitute a highly accurate **detection system for female carriers of the trait for classic hemophilia.** Institute-initiated demonstration projects are currently reporting successful applications of this method in a diversity of settings. This new capability should greatly aid genetic counseling, help reduce incidence of hemophilia in the population, relieve anxiety in potential carriers, and reduce the hardship that hemophilia causes in afflicted families.
- Significant advances have been made in **basic knowledge of the biochemistry of the molecular complex Factor VIII.** It is now known that Factor VIII consists of procoagulant activity and platelet-related activity. Progress in determining further the structure and mechanism of action of Factor VIII should now be facilitated.
- In collaboration with the Health Services Administration, the Institute conducted a **study to determine whether the demand for Factor VIII and Factor IX** would exceed supply through 1980. A public law had been enacted to authorize the expenditure of funds to increase blood separation activities and encourage fractionation if the fractionation products needed by hemophiliacs were not sufficient to meet the need. The study concluded that the demand will grow only moderately each year and that the supply will be adequate.
- It has now been demonstrated that **von Willebrand's disease** (a more common though less serious bleeding disorder than the hemophilias) is **not a platelet or vascular disorder.** Rather, it is a disease caused by an as yet unidentified malfunction of the Factor VIII complex, which in turn results in a defect in platelet aggregation—an important step in normal hemostasis.
- Clinical trials to evaluate the efficacy of **aspirin in the prevention of atherosclerosis and postoperative pulmonary embolism** and in reducing the complications caused by oral contraceptives are being conducted. A prospective clinical trial of the effectiveness of several drugs (e.g., warfarin, dextran, aspirin, and subcutaneous heparin) in the prevention of thromboembolism in patients undergoing total hip replacement is also being conducted.
- A major event in the field of heart disease has been the suggestion that **blood platelets have a major function in both the genesis of atherosclerosis and its clinical manifestation, infarction.** Apparently when the endothelial cells lining the artery die or are abraded, platelets plug the gap until new endothelial cells grow in place. A current theory is that adhering platelets release growth factors that stimulate intimal muscle cell growth and proliferation which, in turn, lead to the infiltration of blood lipids that produce atherosclerosis in the susceptible individual.
- Rapid progress has been made in the **diagnosis and treatment of deep-vein thrombosis,** an acute and often life-threatening disorder. The development of radioscanning techniques using iodine-labeled fibrinogen has been a major advance, since fibrinogen localizes in clots. This technique can now be used almost routinely with hospital patients. Doppler sound-scanning techniques that measure impaired blood flow have also been incorporated into routine clinical use in the last five years. These two techniques combined have had a significant impact on the reduction of the morbidity and mortality of postoperative complications from major surgery.
- **Understanding of the regulation of the coagulation scheme** has progressed markedly. A major question has been, "When blood starts to clot, what stops it from clotting completely?" It is now known that the system is

modulated by inhibitors of clotting factors, the most important of which is antithrombin III, or heparin cofactor. The mechanism of this protein inhibitor was clarified at some of the thrombosis SCORs and this line of research has been fundamental to the development of low-dose heparin therapy.

- **Low-dose heparin therapy** for the prevention of deep-vein thrombosis and pulmonary embolisms has revolutionized the clinical management of these disorders. Heparin given before surgery or to immobilized patients has been shown in several clinical trials to reduce the incidence of deep-vein thrombosis and possibly that of pulmonary embolism. This new therapy is now being introduced into standard medical treatment.

The past five years have been notable for important and numerous advances in biochemical research of bleeding and clotting disorders. In addition, many of these findings have been translated into successful clinical trials or widely accepted therapies for the prevention, early detection, and treatment of bleeding and clotting disorders.

State of the Science in 1977

The progress of the past five years has yielded new fundamental understanding from which both optimism and direction for new research naturally evolve. Although basic discoveries have advanced understanding of the biochemical process of blood coagulation and the disorders associated with it, much remains to be learned.

The understanding of the extreme complexity of the normal hemostatic process at the molecular level is much more sophisticated than it was in 1972. There is a better appreciation of the nature of breakdowns in the normal process and a more integrated approach to both basic and clinical research. Sophisticated biochemical research has produced much data on the complex structure, function, and mode of action of circulating inhibitors of activated clotting factors for blood clot formation. How these inhibitors turn off the clotting system once it has fulfilled its task is now better understood at the molecular level. This understanding paves the way for the development of improved anticoagulant drugs.

The molecular interaction of anticoagulants such as heparin and aspirin has been determined, thus providing a rational basis for their use in the prevention and treatment of thromboembolic disease.

Those surgical procedures that are more likely to cause postoperative deep-vein thrombosis have also been identified. Two new techniques, presurgical administration of minidose heparin and postsurgical monitoring with radioscanning and Doppler sound-scanning, are now being successfully used to prevent or rapidly detect and treat this disorder. These techniques have been incorporated into routine clinical use in the past five years.

The Factor VIII molecule has been purified and partially characterized. This increased understanding of the structure and mechanism of Factor VIII should lead to better methods of treatment of hemophilia and von Willebrand's disease. Understanding is needed of the entire physical, mental, and social pathology of hemophilia. Improved techniques for detecting female carriers of the hemophilia trait can now be translated into genetic counseling programs that could lead to a decrease in the incidence of this disease. Improved replacement therapy allows the hemophiliac to enjoy home therapy and greatly decreases morbidity due to delayed therapy. Progress in treatment of patients who develop inhibitors to transfused Factor VIII has also been made through a cooperative clinical study mounted by NHLBI.

The complex nature of thrombotic problems requires an interdisciplinary research approach. The three Specialized Centers of Research on Thrombosis will continue to provide this multidisciplinary focus of resources, facilities, and manpower to improve the diagnosis, treatment, and prevention of thrombotic and bleeding disorders.

The most promising advances of the past five years have been in discovering more of the complex process involved in the hemostatic system. Each pursuit of a disease-oriented problem has in turn led to a greater understanding of the normal system. Research in bleeding and clotting disorders remains one of the most complex and therefore challenging areas in modern medicine. The questions remain numerous and difficult; the answers are both interrelated and also of utmost importance to the health of Americans.

Program Goals: 1978–1982

Advances in basic understanding of the coagulation system are critical to reduction of the incidence of disability and death from occlusive arterial and venous thrombosis, to the alleviation of symptoms of hemophilia, and to the development of effective therapy for congenital and acquired platelet disorders. To make these therapeutic improvements a practical clinical reality the Institute has established four basic goals to guide its research activities for the next five years:

- Improve the diagnosis of, and therapy for, arterial thrombosis and the various clinical sequelae of this disease process in order to bring about its ultimate prevention.
- Enhance the basic knowledge of venous thrombosis in order to provide improved prophylactic therapy and patient care.
- Develop better understanding of the genetic and pathological mechanisms underlying hemophilia and other bleeding disorders in order to develop improved diagnostic techniques and specific treatments. For those coagulation disorders which are acquired, not inherited, develop better methods for identifying and detecting individuals at risk.
- Increase the general understanding of the role of platelets in the mechanisms of bleeding and clotting and develop more effective therapy for individuals suffering from congenital and acquired platelet disorders.

Research Activities: 1978–1982

Progress to this time allows the Institute to plan much more specific and targeted research activities for the next five years. While the areas of investigation are, in large part, the same as, or similar to, those determined in 1972, the activities planned for 1978–1982 reflect a more advanced knowledge of the specifics involved in the coagulation system, the molecular action of Factor VIII, the detection of thromboembolic disorders, and the clinical application of anticoagulant therapy.

Continuing research efforts:

- Investigation of the structure and function of protein coagulation factors.
- Determination of the function of Factor VIII and clarification of its role in hemophilia, von Willebrand's disease, and thromboembolic states.
- Studies of the immunologic, epidemiologic, and molecular mechanisms through which hemophiliacs develop inhibitors to Factor VIII.
- Research on the biochemistry, structure, and function of the platelet and on the phenomena related to platelet production.
- Studies to correlate *in vitro* platelet function testing and *in vivo* platelet function.
- Further elucidation of the mechanisms of action of prostaglandins and thromboxanes to determine how the metabolites of arachidonic acid control platelet function.
- A search for drugs which affect platelet action and inhibit thrombosis.
- Evaluation of the clinical use of anticoagulants; professional educational efforts regarding their proper usage.
- Consultation to the Health Services Administration supporting the comprehensive hemophilia clinics and collection of clinical data from these clinics.
- Support for animal models of hemophilia and thrombotic disorders.

Studies to be implemented:

- Investigations designed to clarify biosynthesis of the coagulation factors.
- Clarification of the role of prothrombin complexes in the treatment of patients with Factor VIII inhibitors and identification of the procoagulant substances in these concentrates.
- Standardization of platelet function tests, using the proceedings of a workshop on this subject held in late 1977.
- Determination of the effect of modern treatment in hemophilia beginning with a review of autopsies performed in recent years.
- Clarification of the role of the thrombotic process in atherogenesis.

- Assurance of an adequate supply of animals with hemostatic defects for basic studies on atherogenesis with emphasis on those with von Willebrand's disease.

Studies under consideration for increased support:

- Kinetic investigations of coagulation factors and regulatory mechanisms involving application of the knowledge gained in purified protein systems to whole animal or whole cell systems.
- Determination of whether patients with von Willebrand's disease are protected from atherosclerosis.
- Clarification of the clinical pattern of hemophilia including medical, social, psychologic, and economic factors.
- Elucidation of the interaction between the platelet, Factor VIII, and the vessel wall.
- Investigation of methods of culturing cells of importance to hemostasis including megakaryocytes, endothelial cells, and liver cells.
- Investigation of the factors regulating blood vessel growth and proliferation.
- Studies of the interrelations of diet, platelet function, and atherosclerosis with emphasis on the relationship to arachidonic acid metabolism.
- Investigation of the antithrombin system including chemical, cellular, and physiologic aspects with emphasis on the importance of this system in the regulation of hemostasis and thrombosis.

Schedule

Support for fundamental laboratory and clinical research in the area of arterial thrombosis will continue through FY 82. Specialized Centers of Research on Thrombosis have been reviewed and support will continue for successful centers through FY 80.

Fundamental laboratory and clinical investigation of venous thrombosis will be supported through FY 82. New clinical trials will be initiated as required through FY 82.

Clinical trials in Factor VIII inhibitors will continue through 1978. Investigator-initiated fundamental research, developmental research on coagulation factors and their preparation, and workshops on the supply and use of antihemophilic factors will continue through FY 82 as will the development and testing of new and improved treatments.

Support of fundamental research on platelet biochemistry, the role of platelets in bleeding and clotting disorders, and the development and testing of improved treatments for platelet disorders will continue through FY 82.

Red Blood Cell Disorders

The hemoglobin molecule is located in the red blood cell and is essential for oxygen transport. The red blood cells, unlike other cells, can be easily obtained for study. Although the metabolism of the red blood cell is complex and specialized, it is simple compared with that of other body cells, and yet shares enough common features to serve as a useful research model. Study of the red blood cell and its disorders can yield clues about the metabolic controls and regulation of other, less accessible body cells. Aggressive basic research into disorders of the red blood cell holds the potential for significant advances in understanding the metabolism, membrane structure, and functioning of all body cells.

State of the Science in 1972

The potential benefits of a strong basic research program on the red blood cell were recognized in 1972. There was considerable knowledge of the molecular abnormalities in thalassemia (Cooley's anemia) and its carrier or "benign" state, but methods to prevent it had not been discovered. Thalassemia was known to be an inherited, incurable disease resulting from the defective production of one of the subunits of the hemoglobin molecule which in turn leads to rapid destruction of the patient's red blood cells. Treatment was limited to frequent transfusions which provided temporary relief from anemia but burdened the body with excess iron that could not be eliminated. This iron overload eventually resulted in the death of the patient. In 1972, the expected lifespan of a patient with thalassemia was 20 to 30 years. Although thalassemia occurred

in fewer than 5,000 Americans, usually those of Mediterranean descent, it was believed that basic knowledge of this incurable disease, along with improved methods for detection and treatment, would aid in the prevention and treatment of patients with other hemoglobin disorders as well.

Defects in red blood cell membranes and enzymes were also known to produce anemia by causing premature destruction of the red blood cells. Such defects were relatively rare except for one enzyme disorder, glucose-6-phosphate dehydrogenase (G6PD) deficiency, which was known to occur in about 10 percent of black males and less frequently in males of Mediterranean ancestry and other populations. Most people afflicted with G6PD deficiency are healthy, but could develop anemia with the onset of certain illnesses or if they took any of a variety of commonly used drugs.

It was well recognized in 1972 that learning as much as possible about the membrane structure, function, and intracellular metabolic activity of the red blood cell could improve our knowledge in other areas of medicine and lead to advances in the control, treatment, and prevention of many diseases.

Goals Through 1977

Thalassemia and sickle cell anemia are linked at the fundamental level; hence, programs of research, prevention, education, and control of these disorders were jointly developed. The NHLBI recognized both the wide applicability of basic research on the structure and function of the red blood cell, and the public's need and right to the most efficient application of basic findings to improving methods of prevention, control, and education. Closely coordinated with the program initiatives in sickle cell disease, the Institute's goals in the area of red blood cell disorders were to:

- Continue coordination of efforts with other Institutes at the National Institutes of Health and other Federal agencies working to advance basic and applied knowledge of thalassemia.
- Conduct basic research on the mechanism of hemoglobin synthesis.
- Encourage investigator-initiated research and targeted research on normal and abnormal red cell metabolism, membrane structure, and function.
- Conduct clinical research to determine the effect of transfusion programs, and of the removal of the spleen (an organ that breaks down red blood cells as a normal body function), on the course of thalassemia.
- Improve detection and prenatal diagnosis of thalassemia disease and trait; develop agents to remove the excess iron resulting from frequent transfusions; and evaluate educational methods and develop counseling programs for the prevention and control of thalassemia.
- Establish reference laboratories for the diagnosis and investigation of hemoglobin variants, red cell enzymes, and membrane disorders.

Accomplishments Through 1977

In the past five years, of all the cellular components of the blood, the red blood cell has been the most thoroughly studied. In 1972, with the exception of sickle cell disease, there were only two major research areas in red blood cell disorders—thalassemia and other hemoglobin disorders, and red blood cell membrane and enzyme disorders. By 1977, sophisticated research focused on six separate research areas: thalassemia and other hemoglobin disorders; red blood cell production (erythropoiesis); red blood cell membrane and enzyme disorders; aplastic anemias; hemolytic anemias; and oxygen transport. This program diversification reflects the increased understanding of the complexity and functions of the red blood cell as a result of program efforts. The following are the most important advances in these research areas:

- The development of a method to study the synthesis of hemoglobin in the test tube led to the determination that the **molecular defect** in the most common type of thalassemia, beta thalassemia, **resides in the messenger RNA** (a substance carrying genetic information). This messenger contains the information for the correct amino acid sequence, but

it cannot be transcribed rapidly enough to meet cellular needs. In the normal hemoglobin molecule there are two alpha and two beta chains of amino acids. In patients with thalassemia, the slow transcription of messenger RNA to form beta chains results in an excess of alpha chains that leads to premature red blood cell breakdown. Although these findings do not provide an immediate approach to therapy, they present the target area for future research and a hope of improved therapy.

- Procedures for hemoglobin analysis have been applied and found accurate in the **identification of the carrier state of thalassemia.** Such procedures can be used to identify members of a family who carry the thalassemia trait. Accurate identification should greatly aid genetic counseling, relieve anxiety in potential carriers, and reduce the hardship that thalassemia causes in afflicted families.
- Significant progress has been made in the development and **clinical trial of the iron-chelating agent desferrioxamine.** Desferrioxamine chelates or binds with excess iron to form a complex that can be excreted in the urine, thus relieving the body of iron overload. Since the cause of death in patients with thalassemia is iron loading in both the liver and heart, causing cardiac malfunction, development of effective and nontoxic iron chelators could make it possible to extend the life of thalassemics to that of normal people.
- The **controlling action of the kidney hormone erythropoietin** on red blood cell production has been partially characterized. Greater understanding of this system for production of red blood cells (erythropoiesis) will provide a model system for the study of cellular proliferation and will have practical implications in the diagnosis and treatment of anemias.
- In the past five years, basic and applied research in erythropoiesis have been hampered by the fact that the sole source of crude erythropoietin was the urine of patients severely anemic and suffering from hookworm disease in Argentina. Such a limited supply did not encourage investigator-initiated research in this area. For this reason, the Institute sponsored **the development of two centers for the production of crude erythropoietin** and is now able to distribute supplies sufficient to allow further research in the purification of this hormone. A preliminary report describes a new method of purification which yields a preparation approximately eight times purer than those previously available. The purified hormone will allow for the development of a more accurate clinical assay for the hormone and aid in the diagnosis and treatment of anemias due to failure in erythropoietin production, such as the anemia of chronic renal disease.
- Aplastic anemia is known to involve a failure of bone marrow stem cells (earliest parent cells) to reproduce. This failure causes anemia, bleeding, and infection due to decreased production of blood cells by the bone marrow. **Techniques to study stem cell behavior** *in vitro* through the colonies they produce have been developed. This isolation and the ability to study microenvironmental effects on the proliferation of stem cells should lead to further understanding of stem cell behavior, the nature and cause of their dysfunction, and clues to the natural history of aplastic anemia.
- Investigator-initiated research has **identified abnormalities of red cell membrane proteins** considered responsible for at least one of the hemolytic anemias—hereditary spherocytosis. Other defects in red cell membrane structure and function are now known to involve exchange of electrolytes and changes in lipid function. In immune hemolytic anemia, identification and characterization of destructive antibodies are progressing, and their interaction with the red cell membrane is now better understood.
- Recent development of **equipment for automatic rapid determination of oxygen hemoglobin equilibrium curves** has greatly assisted

research on the transport of oxygen. Various studies have partially clarified the mechanisms by which the red blood cell regulates its own release of oxygen according to tissue needs. An important step in this process was identified. It was discovered that a substance, 2,3-diphosphoglycerate, interacts with the hemoglobin molecule to decrease its oxygen affinity and enhances the release of oxygen to the tissues. Subsequent studies identified the metabolic interactions in response to deoxygenated hemoglobin which result in an increase in 2,3-diphosphoglycerate.

Although the intricate complexity of the red blood cell structure and function challenges our best scientific minds, the progress of the past five years holds promise for further multidisciplinary research advances, professional development and training, and the rapid application of new knowledge to improved health care.

State of the Science in 1977

There has been steady progress in the understanding of normal and abnormal red blood cell metabolism, hemoglobin disorders, and the structure and function of the red cell membrane. A multidisciplinary basic science approach has developed sophisticated methods of separating red blood cell membranes into their various components and again reconstituting them. This advance has contributed to a better understanding of red blood cell functions. Techniques to study the *in vitro* synthesis of hemoglobin and some of its variants have led to remarkble advances that present new questions for targeted research.

With the molecular defects of thalassemia defined and the advantage established of maintaining life by frequent transfusions, the clinical problem of treating this illness now focuses on a better understanding of how iron overload damages tissue and on improved clinical effectiveness of chelation (iron-removing) therapy. Clinical trials to assess the effectiveness of the iron-chelating agent desferrioxamine have started, and work to develop new iron-chelators is being initiated. A suitable experimental animal is needed for these studies. Research into the molecular nature of thalassemia needs to be continued so synthesis by manipulation of cell metabolism might be discovered. This discovery could lead to the amelioration of the effects or to the cure of this presently incurable disease.

A crude material supply of erythropoietin, the kidney hormone controlling red blood cell production, has been developed. Distribution of this supply to investigators allows them to move ahead rapidly to develop a purified preparation that can be used clinically for diagnosis and therapy. In addition, protein chemists have begun to characterize the structure of this hormone, and advances in the understanding of cellular proliferation will be forthcoming.

Since 1972, the understanding of aplastic anemia has been largely based on studies in erythropoiesis. Scientists are now able to observe *in vitro* the environmental effects of various bone marrow factors on stem cell proliferation. The precise nature of their influence is, however, poorly understood. Although advances in bone marrow transplantation have offered limited success in the treatment and cure of select patients, further understanding of the behavior of stem cells, the cause and nature of their dysfunction, and the natural history of aplastic anemia is required to develop more effective and less drastic therapies.

Intensive study of the red blood cell during the past five years has led to identification of defective membrane functions and structures resulting in diseases such as hemolytic anemia. Continued multidisciplinary research on the biochemistry and function of the red cell membrane and on the metabolism of the red blood cell in normal and diseased states is required to advance the knowledge of cellular dysfunction in general and of the specific disease state, hemolytic anemia.

Basic research in oxygen transport has advanced the understanding of how the red blood cell appropriately regulates oxygen release to meet tissue needs. Additional clinical and multidisciplinary research are required. This field provides an opportunity as well as a need for cooperation among a variety of NHLBI program areas.

These important advances place the study of the red blood cell at a point where further improvement in the understanding of its biochemistry and molecular behavior in normal and diseased states can be anticipated. The strong basic research pro-

gram on the red blood cell should lead to advances in the prevention, treatment, and cure of red blood cell disorders and to a greater understanding of the metabolism, membrane structure, and function of other body cells.

Program Goals: 1978–1982

The overall goal of the program for the next five years is the development of new knowledge relevant to improving patient treatment, and to extending the lifespan of those afflicted with thalassemia, aplastic anemia, and refractory anemia as well as improving the health status of those afflicted with the various hemolytic anemias. Specific goals are to:

- Devise improved treatment for those already afflicted with thalassemia. Major effort will be devoted to identification of carriers through effective screening.
- Develop knowledge of the underlying causes of aplastic and refractory anemias so as to permit improved treatment; develop information concerning the natural history of these diseases.
- Further elucidate red cell membrane structure, function, and intracellular metabolism to provide information which may be utilized to improve the health status of patients afflicted with the various hemolytic anemias.
- Improve overall knowledge of the crucial role of the red blood cell in oxygen transport through studies of the mechanisms of control of oxygen exchange.
- Develop erythropoietin preparations suitable for use in controlling human diseases.

Research Activities: 1978–1982

Advances during the past five years have not only contributed to our capability to define much more specific areas for targeted research but place us at the point where investigations can lead to improved methods for control and prevention of red blood cell disorders.

The five-year projections listed below represent our current state of knowledge and the most promising avenues for targeted research. As investigations progress, new initiatives will surely evolve and be incorporated into this plan.

Continuing research efforts:

- Studies of the molecular and clinical aspects of thalassemia, especially the use of iron-chelating agents.
- *In vitro* and *in vivo* studies of the function and characterization of stem cells.
- Purification of erythropoietin through application of modern purification techniques.
- Studies of the chemistry and function of the red blood cell membrane.
- Investigations of molecular and nutritional aspects of folic acid and vitamin B_{12}.

Studies to be implemented:

- Epidemiologic investigations of thalassemia.
- Utilization of pure erythropoietin to develop and improve assays for clinical use.
- Coordination of efforts to study the structure and function of the red blood cell membrane in health and disease.
- Research on *in vivo* aspects of oxygen exchange at the capillary level in animals and man.
- Clinical investigations of erythropoietin in selected disorders such as chronic renal failure.

Studies under consideration for increased support:

- Investigations of the activity of pure erythropoietin, as it becomes available in cell culture and whole animal systems.
- Clarification of the significance of various degrees of iron deficiency.
- Application of results of stem cell research to clinical bone marrow transplantation.

Schedule

Basic and clinical research on thalassemia will continue with special emphasis given to studies of the clinical management of the disease during FY 78 and FY 79.

Support for fundamental research on red blood cell production will continue with major emphasis

on the search, which was initiated in FY 77, for additional urinary erythropoietin sources and supplies. New research directed toward the purification of erythropoietin, also initiated in FY 77, will be continued through FY 82.

Investigator-initiated research on basic mechanisms in aplastic anemia will be supported through FY 82. Cooperative studies are anticipated which will be continued through FY 82.

Workshops to develop approaches for study of the basic mechanisms of hemolytic anemias are planned for FY 78. Plans developed through these workshops will be implemented during FY 79 through FY 82.

Fundamental and clinical studies of oxygen transport will continue through investigator-initiated projects. Efforts during FY 78 and FY 79 will emphasize *in vivo* studies of oxygen exchange.

Sickle Cell Disease

Sickle cell anemia is a hereditary disorder of the red blood cell. To inherit the disease an individual must receive the gene for sickle hemoglobin from both parents. Individuals who receive one gene for normal hemoglobin from one parent and one gene for sickle hemoglobin from the other parent inherit the trait, not the disease, and are carriers. There are rarely any clinical problems associated with the trait, but these individuals, as carriers, can pass the sickle cell gene to their offspring. If two carrier jndividuals have children, there is a one-in-four chance with each pregnancy of having a child with sickle cell anemia. Approximately one out of every 500 black Americans has sickle cell anemia, whereas one in every 12 has the trait.

For some time, scientists have understood the hereditary defect in the sickle hemoglobin molecule responsible for sickle cell anemia. In the normal adult hemoglobin molecule (hemoglobin A), there are two alpha and two beta chains of amino acids. These alpha and beta chains are forms of proteins called globins. In the sickle hemoglobin (hemoglobin S), valine is substituted for glutamic acid at the sixth position in the beta chain. This single key amino acid substitution, under conditions of reduced oxygen, results in a tendency for hemoglobin S to aggregate into rigid rods or tubules within the red

In sickle cell disease, the naturally round red blood cells become distorted, often assuming a sickle shape. These sickle cells are rigid and tend to stack up in the small vessels, constricting blood flow and causing severe pain.

blood cell. This aggregation of hemoglobin S inside the cell causes the entire red blood cell to become crescent or "sickle"-shaped and rigid. These sickled and rigid cells are unable to move as easily through the smaller blood vessels and therefore have a tendency to "stack up" and occlude these vessels. The occlusion impairs blood flow and causes spontaneous recurrent bouts of debilitating pain called "crises" and acute or chronic damage to various tissues and organs. In addition, the sickled red blood cells have a shortened lifespan and are destroyed at a rate greater than the bone marrow can produce new red blood cells. Thus, the individual with sickle cell disease is chronically anemic.

State of the Science in 1972

In 1972, despite precise knowledge of the genetic change involved in forming hemoglobin S, scientists were unable to provide effective therapy to shorten or prevent crisis episodes, or to cure sickle cell disease. Necessary basic information on the biology of the red cell, the mechanisms involved in sickling, and the possibility of reversing it, as well as the techniques for early and efficient detection and therapy were lacking.

The character and severity of the manifestations of the disease varied greatly and the reasons were as yet unknown. Some patients could be completely free of serious illness, others over the years suffered organ and tissue damage such as stroke, lung damage, infarcted spleen, destroyed hip joint, leg ulcers, kidney failure, enlarged liver, and bleeding inside the eye.

The life expectancy of patients with sickle cell anemia was also variable. Some patients died at an early age, often due to childhood infections complicated by the disease, while others could lead productive lives until an advanced age.

The general public and many health care providers had limited or inaccurate information about the disease. An aggressive and innovative professional and public education program was needed to disseminate information, to initiate and expand participation of communities in screening and counseling activities, and to improve clinical care of all patients. In 1972, the new Sickle Cell Disease Program along with its emphasis on fundamental research offered the focus and impetus for these educational activities.

Goals Through 1977

The Institute, recognizing the need to stimulate basic research and launch an effective public and professional education program, established the following goals:

- To increase basic and clinical research, clinical applications, clinical trials, training and education, and efforts in screening, counseling, rehabilitation, and information dissemination.
- To better understand the molecular structure of sickle hemoglobin, interactions of other abnormal hemoglobins with sickle hemoglobin, differences in flow patterns between normal and sickle red cells, and the effect of various agents (such as urea and cyanate) on the sickling process.
- To develop simple and accurate techniques for the early detection of sickle hemoglobin abnormalities.
- To develop collaborative efforts with other Institutes of NIH and other Federal agencies.

Accomplishments Through 1977

From its start in 1972, the NHLBI Sickle Cell Disease Program has comprised a coordinated program of diagnosis, education, treatment, and research. Advances have been made in each of the areas. Significant advances include the following:*

- **Fifteen Comprehensive Sickle Cell Centers** were established to concentrate resources, facilities, and manpower in a coordinated approach to solving the multiplicity of problems related to sickle cell disease. These Centers attempt to bridge the gap between scientific investigations and patient care needs.

* Advances related to Education and Counseling Programs and Screening and Education Clinics are discussed in the section on prevention, education, and control.

- By use of x-ray crystallography, electron microscopy, and nuclear magnetic resonance, scientists have determined the **structure of the normal and sickle hemoglobin molecule.** This allows for more sophisticated techniques to be applied to the characterization of the hemoglobin S aggregation. A better understanding of the physical-chemical nature of the sickling process may provide ways of modifying the reaction at the molecular level, which would afford effective therapy for the sickle cell anemia patient.

- A notable accomplishment has been the finding that, of all **antisickling drugs** investigated, **cyanate is the most promising.** *In vitro* studies of the effect of cyanate on sickling have shown that it most likely increases the oxygen affinity of hemoglobin S, thus preventing deoxygenation and consequent aggregation and sickling. Since studies to date indicate that cyanate has serious toxic side effects, techniques are now being developed by which cyanate can be administered by extracorporeal techniques. Some of the patient's blood is withdrawn and treated with cyanate outside the body and then reinfused into the patient after free cyanate has been removed. Preliminary data indicate that this treatment could reduce the severity of anemia and the frequency of crises without significant side effects.

- Particular emphasis has been put on the **synthesis of fetal hemoglobin** in human red blood cells. Fetal hemoglobin does not contain the beta chain in which the genetic substitution responsible for sickle hemoglobin takes place. The synthesis of adult hemoglobin progressively replaces fetal hemoglobin within the first six months of life. This physiologic "switch" mechanism is not clearly understood. However, the possibility exists that increased levels of fetal hemoglobin may eliminate or at least ameliorate the symptoms of sickle cell disease. Therefore, increased knowledge about the "switching" from fetal hemoglobin to adult hemoglobin, and the possibility of either reversing this "switch" or continued synthesis of fetal hemoglobin could provide an approach to effective therapy for individuals with severe sickle cell disease.

- An essential element in sickle cell programming is **accurate and definitive diagnosis.** Proficiency testing by the Center for Disease Control and training programs for laboratory personnel have resulted in a high degree of accuracy and definitive diagnosis of all hemoglobin types. A number of Sickle Cell Centers now serve as reference laboratories for positive identification when samples are too difficult to diagnose in local laboratories.

- It is now possible through improved diagnostic techniques to accurately **diagnose sickle cell disease at birth.** Although the major type of hemoglobin present at birth is fetal hemoglobin, there is also a small percentage of adult hemoglobin present. Despite the presence of large amounts of fetal hemoglobin, hemoglobin S can now be detected in the small amount of adult hemoglobin present in cord blood of newborns. Detection of sickle cell anemia in the newborn has tremendous advantages for the clinical management of the disease. The alerted physician is then able to closely monitor the child for early symptoms of often life-threatening infections.

- The diagnosis of sickle cell disease can be made from fetal blood *in utero,* but current methods of obtaining fetal blood have considerable risks. The development of a flexible fetoscope will make it possible to obtain fetal blood under direct visualization, thereby increasing the accuracy and safety of the procedure. The capability of **prenatal diagnosis** will greatly increase the options genetic counselors can offer couples at risk.

- Clinical research activities have included **evaluation of emergency room procedures for patients with sickle cell crises** or other complications. Because complications are often not recognized or are sometimes misdiagnosed, a protocol has been developed which highlights the symptoms and discusses various diagnoses and treatments. Use of the pro-

tocol has improved emergency room care in a test hospital. The protocol is now being made available to other medical centers throughout the country.

State of the Science in 1977

The NHLBI supports a variety of activities aimed at reducing the frequency, morbidity, and mortality of sickle cell disease through research, improved diagnosis and treatment, and education activities. These activities comprise a coordinated program of basic and clinical research; Comprehensive Sickle Cell Centers; Screening and Education Clinics; education services; and a hemoglobinopathy training program.

The Comprehensive Centers Program has created a unique concept in approaching health problems and has proved to be an effective model that embraces the needs, opinions, and participation of the client population and provides a positive interaction with the academic and scientific communities.

Today, although there is no cure for sickle cell disease, many more individuals at risk have been identified and are provided with information and supportive counseling necessary for them to consider their options freely.

To determine why manifestations of the disease vary from individual to individual, a cooperative study of the clinical course of the disease and its effect on the major organ systems is being initiated.

The biomedical research program has contributed to the advancement of our understanding of sickle cell disease through molecular, cellular, tissue, and organ studies. We are now able to detect sickle cell disease in the newborn and soon will be able, with the refinement of a new fetoscope, to advance to prenatal detection. Important new research projects include an attempt to understand and clarify the molecular conformation of sickle hemoglobin and its interactions in the oxy- and deoxy- states; the study of cell membrane changes during sickling; the augmentation of fetal hemoglobin in red blood cells; investigation of viscosity and flow properties; and the role of clotting factors in the painful crisis.

Most critical of all is the continuing attempt to find an effective, nontoxic, antisickling agent that is able to control or prevent the serious vascular complications of sickle cell anemia. Efforts to develop an animal model to study the microcirculation in sickle cell anemia could facilitate these investigations. Meanwhile, further development of extracorporeal techniques, including testing of a machine for continuous flow carboxylation of whole blood, will allow scientists to study the effect of cyanate on sickling in a more controlled manner and will also serve as an approach for the administration of other similar therapeutic agents.

The existing educational efforts of the National Program have been broadened through the support of non-governmental organizations to carry out programs in public awareness, aid in the dissemination of factual information, and conduct educational programs in sickle cell disease throughout the country. Innovative materials and methods are being developed and tested for these purposes. The target audience for these efforts includes health providers, employers, insurance companies, health educators, and persons with sickle cell trait or anemia.

The progress of the past five years is a witness to the wisdom of concentrating a national focus on basic research, clinical treatment, and public and professional education on sickle cell anemia. This progress enables the program to appreciate anew the complex research and social issues involved in the challenge to treat and someday cure sickle cell anemia.

Program Goals: 1978–1982

To fulfill its mission to reduce morbidity and mortality due to sickle cell disease and to translate "state-of-the-science" conceptualizations into universal practice, the NHLBI has established the following goals:

- To continue basic research into the pathophysiology of the disease process at the molecular, cellular, and clinical levels.
- To develop improved methods of clinical care.
- To develop a more rational approach to patient management, based on the latest scientific advances.

Research Activities: 1978–1982

Improved clinical management of individuals with sickle cell disease requires a sound basic research program and a concerted effort to educate the practitioner in the community. To this end the program has planned and is already conducting a number of research activities.

Continuing efforts include:

- The elucidation of the intermolecular contacts of the HbS fiber by the use of a variety of techniques which include:
  - Fiber x-ray diffraction studies with major emphasis on obtaining fiber patterns with more ordering.
  - Spectroscopic techniques including high-resolution nuclear magnetic resonance and various spectroscopic probe methods.
  - Study of the gelling properties of chemically modified HbS and genetically modified hemoglobins.
  - Single crystal x-ray diffraction studies to define the three-dimensional structure of the oxy- and deoxy- forms of HbS.
- Studies on the equilibrium and kinetic aspects of the factors that affect gel formation.
- Development of techniques for studying the mechanisms of the switch from fetal to adult hemoglobin production.
- Molecular studies aimed at the delineation of the regulation of globin gene expression in general as well as the gamma and beta loci, specifically.
- Studies to define the cellular regulation of gene activity in differentiating cells.
- Studies of humoral and cellular immunity.
- Studies on metabolism of sickled cells, such as development of incubation systems which more closely simulate human intravascular and tissue conditions and permit controlled perturbations of pH, PO_2, and temperature.
- Development of new and better inhibitors of polymerization of HbS.
- Determination of the pathophysiology of sickle cell disease. While the major abnormality in sickle cell anemia is stasis of the red cells in the microvasculature, it is not yet possible to quantify this process.
- Development of an integrated study to collect uniform data on the clinical course of sickle cell anemia.
- Studies to assess the role of coagulation in the pathogenesis of vaso-occlusive crises.
- Evaluation of the use of hypertransfusion therapy both prophylactically and in the treatment of crises.
- Development of safe and effective techniques of fetal blood sampling for the prenatal diagnosis of sickle cell anemia.
- Development of extracorporeal techniques for administering drugs to circumvent toxicity and to permit further study of potential drugs in a more controlled manner.

Studies to be implemented:

- Evaluation of potential therapeutic agents for sickle cell disease.

Schedule

The studies listed under continuing efforts are ongoing and will be continued through FY 82, with the exception of studies to assess the role of coagulation in the pathogenesis of vaso-occlusive crisis. These are currently in progress and should be completed in FY 80.

Evaluation of potential therapeutic agents for sickle cell disease will begin in FY 78 and continue through FY 82.

Blood Resources

Blood resources, the nation's supply of blood and blood products, are so critical to the health of Americans that in 1974 the President declared it a national resource. Whole blood contains red blood cells, white blood cells, and platelets suspended in plasma. Most whole blood is collected by an assemblage of organizations which might be referred to as the blood service complex. Currently, in excess of 10 million units of whole blood and 3.4 million liters of blood plasma are collected and used for therapy in the United States each year. Because safe and

Scanning electron micrograph of a normal red blood cell.

adequate supplies of blood must be available, the optimal management and utilization of this national resource are vital to the improved health care of the nation.

Transfusion of red blood cells is important in restoring the normal oxygen-carrying capacity of the blood in patients acutely anemic as a result of hemorrhage or chronically anemic because of diseases interfering with normal red cell production. In general, the demand for red blood cells for use in transfusion therapy exceeds that of any other single blood component.

White blood cells are vital to the body's defense against infection. In cancer, leukemia, and certain allergic states, circulating leukocytes (a type of white blood cell) are frequently diminished in quantity or impaired in functional quality. As a result, the patient is susceptible to serious infections that may not respond to antibiotic treatment. Transfusions of white blood cells may be beneficial in such cases.

Platelets play a prominent role in the initiation of coagulation and in the maintenance of the blood vessel integrity. Leukemia patients often have low circulating platelet levels, either as a result of the disease itself or as a toxic reaction to the drugs used in treating the disease. Drug treatment of solid tumors also frequently reduces platelet levels. Such platelet deficiencies can result in serious, often fatal, hemorrhage. Platelet transfusions are vital for these patients.

Plasma is collected mainly for the preparation of plasma protein fractions such as serum albumin used to treat shock; blood grouping protein needed for blood typing; gamma globulin for antibodies to fight disease; and antihemophilic globulin to reduce bleeding in hemophiliacs.

Transplantation biology is the grafting of tissues or organs from one place in the body to another or from one body to another. The immunoallergic response of the body is to reject such grafts. Knowledge of this response, a better understanding of immunology and immunogenetics, and advances in organ and tissue typing and storage are essential to success in transplantation biology.

State of the Science in 1972

By 1972, about 9 million units of blood and 3.0 million liters of plasma were collected each year. Despite this seemingly large supply, poor management and limited technology resulted in a supply of blood that was sometimes inadequate and at other times in excess of requirements. No one knew what the nation's seasonal needs were nor what the distribution of the existing supplies was so that they could be maximally used with minimum wastage.

The collection process usually took place in local hospitals. There was no uniform method of blood collection or standard criteria for its use. Whole blood was used in three-fourths of transfusions although it was needed in less than one-fourth of those cases. Other blood components could have been separated out and were in high demand: Factor VIII and Factor IX were needed to treat hemophilia; gamma globulin was needed to prevent infectious diseases; and platelets were needed to restore clotting ability in patients with leukemia or aplastic anemia. However, no system existed either to monitor the use of whole blood or to effectively advance and disseminate information on the methods and indications for the use of specific blood components. Moreover, improved technology was required to extend the shelf life of blood components and to make the fractionation (separation) of the components more efficient and less expensive.

The safety of blood transfusion was also an issue of great concern in 1972. There was no means for detecting transmissible diseases in donor blood and, consequently, hepatitis and cytomegalovirus diseases killed hundreds of patients receiving transfusions, and caused thousands of episodes of illness and hundreds of thousands of infections. The human cost in suffering was immeasurable; the health care costs were in the millions. Another safety issue, the development in the recipient of a sensitization to transfused histocompatibility antigens (HLA), rendered further transfusions useless. A method for removing the antigens needed to be developed if patients dependent on frequent transfusions for life were to survive.

Blood was manually typed and matched. Human error was a major hazard. The paid donor also presented a major safety problem. Although only 10 to 15 percent of blood was collected from paid donors, that blood accounted for one-quarter to one-half of the incidence of post-transfusion hepatitis. While volunteer donor motivation was only partially understood, it was felt that the development of an all-volunteer blood donor system could go far toward decreasing the incidence of post-transfusion hepatitis. Another solution, development of artificial blood substitutes, was conceptually sound, but in 1972 it was only in its initial exploratory stages.

In transplantation biology more fundamental knowledge in immunology and immunogenetics was needed before transplantation could be used more widely and more successfully. It was also acknowledged that we needed improved means to manage the transplant patient. No national or regional system of organ procurement existed. Before such a system could be established, the ethical, legal, and moral questions involved needed to be addressed publicly.

In short, in 1972 our national blood resources represented a complex and fragmented system that was inadequately regulated, unplanned, and sometimes poorly managed. The consequences were often the inefficient use of a limited blood supply and compromised quality and safety.

Goals Through 1977

Despite the serious shortcomings, the blood service complex had enormous strengths and, in the main, had served the American people well. The Institute recognized this as well as the need to develop a system to assure an adequate and accessible supply of high quality blood and blood components by using the national blood resources with maximum efficiency, economy, and safety. Therefore, in 1972 the Institute set the following goals:

- Facilitate coordination of Federal, public, and private organizations involved in blood banking for the purpose of creating policy and procedures for a regionalized, nationwide blood system, entirely supplied by volunteers.
- Create a National Blood Data Collection Center to provide comprehensive and continuous information on the nation's blood supply, size, distribution, and use.

- Identify and describe key operational aspects of the American blood system, including inventory tracking, prediction of blood needs, donor motivation, and expediting the clinical application of new developments in procurement and distribution.
- Participate with other agencies in basic and applied research to detect hepatitis carriers and to eliminate, if possible, the transmission of hepatitis and cytomegalovirus.
- Develop fail-safe systems for donor-recipient identification.
- Support basic and applied research to improve methods for storage and preservation of whole blood and its components, for making the fractionation of blood more efficient and less expensive, and for establishing and disseminating clearer indications for the clinical use of individual components.
- Encourage fundamental research in immunology and immunogenetics and initiate clinical studies to prevent graft-host reaction in transplantation biology.
- Encourage efforts to develop a system of organ procurement on a regional and national basis.

Accomplishments Through 1977

The five years since the Institute participated in the establishment of a National Blood Policy have been marked by a steady growth in our understanding of the operation of our current system and its potential for improvement. Program initiatives have led to advances in basic knowledge and technology. The more important steps in this progress are as follows:

- NHLBI collaborated with the Bureau of Biologics of the Food and Drug Administration (FDA) and the private sector of the blood banking community to **develop the National Blood Policy and help establish an American Blood Commission (ABC)** through which the private sector in blood banking will develop plans for implementation of the National Blood Policy.
- In addition to assisting in the creation of the ABC, the Institute has **supported research conducted by ABC task forces** in the following areas: the regionalization of blood bank services; the national blood data system; the Committee on Commonality (development of standard and machine-readable labels for blood products and of other automated methods); and donor recruitment.
- A three-year analysis of the complex and fragmented blood supply system led to the **design and initiation of a national blood resource information system** based on standardized reporting applicable to the blood banking community. Supported in collaboration with the Bureau of Biologics of the FDA, this system, **Blood Establishment Inspection and Registration System (BEIRS),** will contain descriptive information about national blood resource establishments including practice, record standards, and personnel. BEIRS will integrate its information with that of a proposed National Blood Data Center. Feasibility studies for this national blood data system are at an advanced stage, and the NHLBI is supporting its establishment through the ABC. Data on cost of blood and blood products and monitoring of national blood inventories and predictable needs will be a part of this system.
- The operating relationships among this country's blood banks, blood centers, and transfusion services have been studied and guidelines formulated to improve their integration into a **more effective "regionalized" system.** A study of 12 diverse regional blood systems is considering potential models for the encouragement of a planned evolution toward a national network of regional blood centers. A recent workshop co-sponsored by the Institute and the Bureau of Biologics explored the possibility of **regional licensure** of blood services. These proceedings have been widely distributed.
- A new **National Research and Demonstration Center** in blood resources was established in 1975. The center's concern is improved acqui-

sition, processing, storage, distribution, and clinical use of blood and blood products.

- The **discovery of the serum hepatitis antigen** (HBsAg or Australian antigen) and the demonstration of its relationship to human hepatitis type B has opened the way for studies to develop a **vaccine against hepatitis.** Recent work has led to the development of a method for purifying hepatitis virus and associated particles. If this method can be applied to large-scale production of the virus, a vaccine can be prepared for testing its effectiveness and safety in man. This is an effort actively pursued by the National Institute of Allergy and Infectious Diseases. Further Institute support for research in hepatitis detection has culminated in the characterization of the e antigen, a recently discovered soluble antigen that appears to be a better marker for infectivity than Australian antigen.
- A cooperative study on transfusion-transmitted viruses has shown that **type B hepatitis has been largely controlled** as a transfusion complication. More sensitive techniques to identify the hepatitis viruses allowed scientists to discover so-called non-A–non-B hepatitis. This form, previously masked by the high incidence of the other two types, is now known to be as common as the other two were before the incidence was significantly reduced. No method to control non-A–non-B hepatitis is presently available, and the generation of new carriers in the community is now known to be largely by oral transmission. It now also appears that genetic factors may increase propensity to the carrier state.
- An **NHLBI-supported chimpanzee colony** is now fully operational and provides an invaluable resource for the advancement of hepatitis research. The chimpanzee is the only known animal model that develops clinical hepatitis B.
- Standardized human and machine-readable labels and codes for blood bank containers and equipment have been developed under contract with the ABC and are now being extensively field-tested. This **fail-safe automated system** could eliminate human error in identifying the donor, blood unit, and recipient.
- During the past four years, **platelet storage** has become feasible in most donor blood banks in a manner similar to that of red blood cells. Recently completed studies indicate that the maximal liquid-state storage period for platelets is three days. Preliminary studies, however, give **promise of long-term preservation by freezing.** Over 50 percent of platelets stored up to six months have retained viability after thawing. This advance, along with improved methods of preservation, could greatly aid therapy for acute leukemia and aplastic anemia.
- Advances in the past five years now make it **possible to type and match blood platelets** in much the same way as red blood cells. Platelet typing has resulted in improved response in patients who have become resistant to unmatched platelets after several transfusions. The typing is of the HLA (histocompatibility) antigens, also known to play a major role in host-graft rejection in transplantation biology.
- Granulocytes, a form of white blood cell (leukocyte), have been thought to be of great therapeutic value for 20 to 30 years. Due to their fragility, however, it has been impossible to separate and store an adequate supply for clinical use. New methods of fractionation (modifications in continuous-flow centrifuge) have significantly **improved granulocyte yield** and allow for their increased use in treating infections, especially in patients with low granulocyte count such as those with acute leukemia, aplastic anemia, neutropenia, and malignant melanoma. With this advance in availability, increased efforts are being made to **improve the shelf life of granulocytes.** They need not be used immediately, but can be stored up to 24 hours, possibly longer.
- The increasing use of serum albumin (the major plasma protein) dictates the amount of plasma that is collected and processed. In

response, the Institute jointly sponsored a workshop to develop **guidelines for the clinical use of albumin.** The guidelines have been published in a medical journal. It is expected that they will be useful in reeducating medical care personnel.

- **Progress in the preservation of red blood cells** has been marked. Two advances are of special importance: the use of **adenine** in preserving solutions and the development of a new **closed system docking device.** Adenine, considered for licensing by the FDA, can extend the out-dating period from 21 to 35 days. This action will improve the product when used at 21 days and increase the opportunity for better inventory management due to the extended out-dating period. Red blood cells can be maintained for many months without quality loss when stored in a frozen state. Present FDA regulations, however, require it to be used within 24 hours once thawed. The new closed system docking device being clinically tested will make it possible for blood bank personnel to thaw red blood cells and selectively remove fractions while maintaining the sterility of the remainder. This substantially increases the safe storage time of all red blood cell products and reduces wastage due to out-dating of products before they can be used.
- Animal transfusion **studies with blood substitutes have been highly encouraging.** Primates have been maintained for several hours with 80 percent of their blood replaced with a synthetic-type substitute. Other animals have been maintained for longer periods with a 90 percent replacement. Animals completely transfused with a natural-type substitute completely recover from the transfusion by replacement of the blood substitute with their own blood and continue to lead normal lives. In the foreseeable future, the blood substitutes will provide an emergency modality in the form of hemoglobin solutions and a tool for new biological investigation with the fluorocarbons. Whether they would ever significantly help to reduce the hepatitis problem and supplement and conserve the national blood supply is speculative at this time.
- Recent studies in transplantation biology have resulted in basic understanding of the **relevance of transplantation (HLA) antigens for kidney and bone marrow transplantation.** Although it is known that HLA matching is important to ensure success of a kidney transplant, data to date also indicate that other important factors are involved. Recent discoveries have demonstrated in some patients the formation of "blocking" antibodies that protect the graft against cytotoxic antibodies and the lymphocytes that are the "killer cells" responsible for graft rejection. The prospect of discovering the mechanism to induce production of blocking antibodies in all patients presents a possible solution to kidney graft rejection.
- **Histocompatibility testing has advanced in complexity** and yields new and potentially far-reaching implications for transplantation biology and for increasing our understanding of the development of certain diseases known to be associated with HLA antigens with a frequency greater than can be explained by chance alone. We are now able to separate out T and B lymphocyte cells, and the serum for typing B cells has been developed. B cells have surface antigens that, under certain circumstances, produce antibodies that may be responsible for stimulating T cells to become the cells responsible for delayed graft rejection of kidney transplants. Studies are in progress to determine whether B-cell matching will improve kidney transplantation graft survival. Kidney transplantation has become a standard treatment for chronic kidney failure.
- **Bone marrow transplantation** is the accepted treatment for severe aplastic anemia and combined immunodeficiency disease when a matched donor is available. Improvement in the supportive care of these patients in the past four years has resulted in a 50 percent long-term survival rate. A major cause of fatality is host-graft rejection. Preliminary studies in dogs suggest that it is possible to

remove the cells responsible for graft-versus-host disease from the marrow before it is transplanted.

- **A bone marrow registry has been established** and will provide valuable data for further studies on patient survival, risks, and prognostic factors. An increased number of **potential organ recipients have been identified.** To advance toward our goal of a national tissue and organ network, we need to identify potential donors, catalog these entries, and computerize the system.

These advances make it much more likely that the transplantation of major organs will soon be a routine and efficient surgical procedure and all those who need it will receive an adequate supply of high quality blood and blood products.

State of the Science in 1977

Dissatisfaction with the existing blood service complex in 1972 led to the design of a National Blood Policy and progress toward its implementation. In 1972, there was little concrete information on the fragmented, unplanned system. Today several basic studies to analyze the system have been completed and the design of a network of regional centers begun. A systematic assessment of personnel needs has been initiated as well as a National Blood Data System to monitor blood resources, needs, and costs. Significant technological advances in blood safety, storage, preservation, fractionation, and transplantation biology have been made. These technological advances have led in several cases to clinical trials and in some cases to broad clinical application.

Development of any national policy is a delicate and time-consuming process that requires a judicious balance of many community elements: private, government, consumer, organized labor, and, in this instance, scientific and health care delivery systems. Steady progress over the past five years has built up the basic information base to guide us in the implementation of the National Blood Policy. With the establishment in 1975 of the non-governmental American Blood Commission to implement the National Blood Policy, the role of the Institute has been modified to one of key collaboration. The Institute remains, however, the focus of studies on the research and scientific management of the nation's blood resources.

Despite this progress, much remains to be accomplished. The nation still does not have an all-volunteer blood supply; optimum management of the blood supply must be defined and implemented. Recipients still must bear the risk of contracting hepatitis from transfused blood, and generation of new carriers by oral transmission of the virus may increase this risk. Tests to detect carriers of non-A–non-B type hepatitis must be developed. Methods to remove hepatitis viruses from blood products need to be developed. Use of blood substitutes offers tremendous potential for increased safety and conservation of supplies, but this work is in its initial stages. Whole blood is used more often than necessary, and newly developed techniques for blood fractionation, storage, and preservation as well as clear indications for the use of blood components are not well understood by many of the nation's medical practitioners. Although a fail-safe automated system for typing and matching blood is in the field-test stage, human error is still responsible for the majority of mismatches. Much more fundamental knowledge is needed on the histocompatibility system and the process of host-graft rejection before transplantation biology can become low risk. To this end, all investigators have been asked to submit their data so that a combined analysis may be made.

Progress during the past five years has been steady. The next steps are much easier to discern than they were in 1972. The fundamental basis for continued progress has been laid and the outlook for the future is optimistic.

Program Goals: 1978–1982

The mission of the NHLBI in the areas of blood transfusion and transplantation biology is twofold: to assure an adequate supply of high quality blood and blood products to everyone in need, and to advance basic understanding of the immunology and genetics of transplantation biology in order to improve clinical application. Overall goals flow from this mission and will continue to guide the program's development during the next five years. Because this program encompasses five distinct pro-

gram initiatives, the goals and research activities for each of the five program areas will be reported separately.

National Blood Program:

- Foster the efficient use and assure an adequate supply of high quality blood and blood products for everyone in need. Promote more effective planning in the management of the national blood resource through the collection and analysis of national blood resource data.
- Improve the management of our national blood resource through studies of currently operating blood procurement procedures, donor recruitment strategies, current manpower training needs, dynamics of regional supply systems, and methods for promoting the safety of blood service operations.

Blood Safety Program:

- Prevent morbidity and mortality from post-transfusion hepatitis and other transfusion-transmitted infections.
- Eliminate toxic substances from the many surfaces contacted during the collection, processing, storage, and transfusion of blood.
- Produce a universally acceptable system to ensure that the patient receives the designated transfusion.
- Eliminate human errors through the development of automated blood typing and cross-matching instrumentation.

Blood Substitutes Program:

- Synthesize and biologically screen new and improved fluorocarbon compounds for use as artificial blood substitutes.
- Synthesize and test iron-chelate complexes for use in artificial blood substitutes for eventual complete replacement *in vivo* or for the perfusion of isolated organs *in vitro*.
- Prepare a stroma-free hemoglobin solution and make it available for use as a temporary artificial red cell substitute.
- Develop the surfactants necessary to effectively emulsify those classes of fluorocarbons showing greatest potential as blood substitutes.
- Study the biological effects of perfluorinated substances as artificial blood substitutes.

Blood Component Therapy Program:

- Develop definitive guidelines for the clinical use of platelet concentrates for transfusion.
- Determine and clarify parameters of collection and function of leukocytes as related to effective transfusion therapy.
- Clarify guidelines relative to proper use of red blood cells, to maximize their use in place of whole blood.
- Develop new methods of plasma fractionation including the preparation of clinically useful trace components. Support clinical trials for FDA licensure of these new components and methods.

Transplantation Biology Program:

- Maintain the support of an international bone marrow transplantation registry to help evaluate new treatment modality.
- Support activities for testing of cells and tissues aimed at clinical application of histocompatibility.
- Explore the possible role of regional blood centers in the collection, processing, and distribution of human tissues and organs for transplantation.
- Collaborate with other institutes in the maintenance of a national HLA type registry.

Research Activities: 1978–1982

Each of the five program areas listed above has developed a detailed plan of research activities directed toward realizing its goals. These activities are listed by program below.

National Blood Program

Continuing research efforts include:

- The Task Force on "Operating Relationship and Resource Sharing of Blood Banking Services on a Regional Basis."
- The Task Force on "Meeting National Blood Banking Data Needs," through effective plan-

ning to promote more efficient use of the national blood supply.

- Development of the National Blood Data Center to collect data on the national blood resource relative to training needs, collection, and utilization of blood and blood products.

Studies to be implemented:

- A study on "Blood Utilization" in order to encourage the use of blood components or plasma fractions instead of whole blood.

Safety of Blood Therapy

Continuing research efforts include:

- The study of transfusion-transmitted viral hepatitis being conducted in five medical centers.
- Availability of chimpanzees for hepatitis research.
- A study to evaluate the prophylactic ability and treatment potential of hepatitis B immune globulin (HBIG).
- A study for the removal of hepatitis virus from infectious blood and blood products.
- A study of improved hepatitis detection.
- A study using hepatitis B immune globulin to interrupt the vertical transmission (mother to fetus) of hepatitis.

Studies to be implemented:

- Evaluation of the effectiveness of e antigen as a "marker" of hepatitis infectivity.
- Initiation of new studies on the epidemiologic, clinical, and serologic characterization of non-A–non-B hepatitis, the most common cause of post-transfusion hepatitis.
- Development of a new procedure to assure the positive identification of compatible blood for patients.
- Research to determine whether freezing and/or washing red blood cells will lower the incidence of hepatitis in transfused patients.

Blood Substitutes Program

Continuing research efforts include:

- Synthesis and biological screening of new and improved fluorocarbon compounds for use as artificial blood substitutes.
- Testing, in small animals, the effectiveness of new fluorocarbons as temporary blood substitutes.
- Development and testing of oxygen-binding chelates in animals with much of their blood replaced by free hemoglobin.

Studies to be implemented:

- Preparation of a stroma-free hemoglobin for evaluation as a temporary artificial red cell substitute.
- Development of new surfactants necessary to effectively emulsify newly synthesized clinically useful fluorocarbon compounds.
- Research on the biological effects of perfluorinated substances used as artificial blood substitutes.

Blood Component Therapy

Continuing research efforts include:

- Studies on the preservation of human platelets for transfusion.
- Studies on the collection, function, and transfusion of platelets.
- Studies on the collection, function, and transfusion of granulocytes (one type of white blood cell). The results of these studies will be used to develop clinical guidelines for optimal transfusion therapy.
- Development of new methods of plasma fractionation.

Studies under consideration for increased support:

- Studies to examine parameters of filtration and centrifugation systems that affect yield and function in the procurement of leukocytes.
- Studies to determine the effect of leukopheresis on repeat donors to establish guidelines to assure donor safety and to assist in donor selection.

Transplantation Biology

Continuing research efforts include:

- Operation of the International Bone Marrow Registry.
- Basic research in transplantation (HLA) anti-

gens to determine the role and relevance of the antigens for bone marrow and renal transplantation and platelet and granulocyte transfusion.

Studies under consideration for increased support:

- Clinical studies to determine the significance of HLA sensitization in bone marrow transplantation and platelet and/or granulocyte transfusions.
- Studies to provide new methods potentially capable of making blood products "free" of leukocyte antigens.
- Development and production of B lymphocyte typing sera as part of the national blood resource.
- Exploration of the possible role of regional blood centers in the collection, processing, and distribution of human tissues and organs for transplantation.

Schedule

National Blood Program. All the targeted activities that are presently being supported will be completed by FY 82: The Task Force study on "Operating Relationship and Resource Sharing of Blood Banking Services on a Regional Basis" will be completed in FY 79; it is hoped that the National Blood Data Center will be established and in full operation by FY 81; the Task Force on "Meeting National Blood Banking Data Needs" will complete its work by FY 80.

The study on "Blood Utilization" and the accompanying professional education will be completed by FY 82.

Safety of Blood Therapy. All of the studies that are presently being supported will be completed by FY 82: the large transfusion-transmitted viral hepatitis study will be completed by FY 80; funding for the chimpanzee breeding colony will be discontinued after FY 80; the HBIG study will be completed in FY 78; the hepatitis removal study will be completed in FY 78; the hepatitis detection study should be completed in FY 79; the study aimed at interrupting the vertical transmission of hepatitis will be completed in FY 78.

New approaches to the prevention or reduction of morbidity and mortality as a consequence of post-transfusion hepatitis will be initiated during FY 79 and 80: evaluation of the effectiveness of the e antigen, and new studies on the characterization of non-A–non-B hepatitis are among these new approaches.

Support for the development of a new procedure to assure the positive donor-recipient identification will be initiated in FY 79.

Blood Substitutes Program. Studies to synthesize and biologically screen new and improved fluorocarbon compounds are due for completion during FY 78 and FY 79. Basic studies on oxygen-binding chelates will be supported through FY 82.

Support for the preparation of a stroma-free hemoglobin may be initiated in FY 79.

Studies to develop new surfactants will be initiated in FY 79 and supported through FY 80.

Studies to determine the biological effects of perfluorinated substances may be initiated in FY 80 and supported through FY 82.

Blood Component Therapy. The studies on the preservation of human platelets for transfusion were awarded for two to three years and should be completed by FY 80. The studies addressing the problems of collection and transfusion of granulocytes will also be completed by FY 80.

The study to develop new methods of plasma fractionation utilizing polyelectrolytes and affinity resins will be completed by FY 79. The study to prepare a gamma globulin suitable for intravenous administration will be completed by FY 79.

A fractionation center which is capable of custom isolation of proteins and enzymes for investigators is supported through FY 79. Studies resulting from the international workshop on the technology of protein separation will be initiated during FY 79 and 80 and will continue through FY 82.

Studies to examine parameters of filtration and centrifugation systems that affect function and yield in granulocyte procurement will be initiated in FY 79, resources permitting, so will studies to determine the effect of leukopheresis on repeat donors.

5. PREVENTION, EDUCATION, AND CONTROL

With the passage of the National Heart, Blood Vessel, Lung, and Blood Act of 1972, Congress recognized that the greatest promise of reducing the staggering toll of disability and death resulting from cardiovascular, pulmonary, and blood diseases lay in the prevention and control of these diseases and their complications. Accordingly, through that Act, Congress extended the authority of NHLBI to include education and prevention activities.

The Institute's response to this mandate was to develop and implement a three-phased program strategy that established prevention, education, and control activities as the logical steps following the acquisition, development, and practical evaluation of new knowledge along the biomedical research spectrum shown in Figure 2. As this figure indicates, all NHLBI programs relate to prevention and control to some degree, with the prevention and control aspects of these programs becoming more prominent as the research focus moves along the spectrum from the acquisition of new basic knowledge to its application in health care practice.

THE OFFICE OF PREVENTION, EDUCATION, AND CONTROL

Accomplishments Since 1974

To implement the Institute's prevention, education, and control (PEC) program strategy, a specific program office was established in 1974. Since that time, the Office of Prevention, Education, and Control (OPEC) has explored a variety of potential PEC efforts, identified the most fruitful areas for NHLBI activity, sought resources for carrying out those activities, and critically reviewed new programs prior to implementation. OPEC has provided technical assistance to the Institute's programmatic divisions in their efforts to launch PEC programs, and has encouraged and developed cooperative relationships with external agencies and organizations (governmental and private). A system has been developed for tracking the Institute's various research programs to exploit their potential for prevention, education, and control. In addition, Institute professionals have been introduced to the capabilities of the behavioral and social sciences in dealing with health behavior problems. Through a program of visiting lecturers and consultants, behavioral and social scientists have stimulated research in areas of Institute concern.

Examples of specific accomplishments include the following:

- **Disseminated information concerning NHLBI research activities.** Since its creation in 1948, the Institute has placed high priority on the critically important function of translating advances in research and the results and findings of clinical trials to the professional and lay public. This effort includes holding press conferences; producing press releases that are printed by hundreds of daily newspapers and reach an audience of millions; developing brochures, pamphlets, fact sheets, and exhibits for professional and lay consumption; and employing the mass reach of radio

Dr. Robert I. Levy, Director of the National Heart, Lung, and Blood Institute, addresses members of the press on significant findings from the Lipid Research Clinics.

and television specials and public service advertising to keep the Institute's activities and progress before the American public.

- **Established cooperative relationships** with a number of professional societies, professional organizations, and special interest groups to inform them of the interests and concerns of the Institute and to encourage behavioral and social scientists to undertake research in Institute priority areas.
- Played an integral role in the proceedings and recommendations of **four behavior-oriented conferences** that have served as the impetus for initiating behavioral research.
  - The symposium on *Applying Behavioral Science to Cardiovascular Risk* examined the state of the art of behavioral science in contributing to health behavior in general and to reducing the risk of heart attack and stroke in particular. The proceedings gave evidence of an increasing ability on the part of behavioral scientists to provide intervention strategies capable of influencing health behavior on a large scale.
  - The *Nutrition-Behavioral Research Conference* reviewed the objectives, progress, and results of each of the NHLBI nutrition, education, and intervention programs; assessed other research in the area; and recommended methods for producing dietary behavior changes in specific target populations.
  - The *National Conference on Emotional Stress and Heart Disease* attempted to define and correlate emotional stress with the pathophysiology of the human cardio-

vascular system, with emphasis on sudden death and myocardial infarction.

- The *NHLBI Working Conference on Health Behavior* (1) made behavioral scientists aware of Institute needs, priorities, and concerns in the area of health behavior; and (2) provided Institute scientists with substantive information and advice on health behavior problems related to prevention and control of heart, lung, and blood diseases. Several program initiatives resulted from the recommendations of this conference, and a number of small working groups were established to investigate such areas as health maintenance behavior, behavioral approaches to the treatment of hypertension, and behavioral factors associated with the etiology and prevention of hypertension.

- **Influenced, directly and indirectly, continuing medical education (CME)** to effect the organization of a professional association for the Directors of CME of American Medical Schools; the creation of a task force of the Association of American Medical Colleges to develop a medical school training program in response to the new demand for CME; development of model CME systems for use at the state level; creation of a model medical practice act linking licensure to competence; and the convening of a national conference on competence assessment and licensure.

- **Established the Visiting Scholar Program** to bring outstanding behavioral scientists to the Institute to share their expertise with NHLBI staff members during a monthly colloquium, and the **Resident Scholar Program,** which brings scholars to the Institute for one year to increase their familiarity with Institute priorities.

- **Initiated a mini-conference system** in which a single issue is explored by a small, select group of outside consultants in order to assist in clarifying the Institute's role in topics such as behavioral medicine and coronary-prone behavior.

- **Initiated a study of the process by which results of biomedical research and clinical trials are translated into field application.** Historically, the impact of clinical trials on the practice of medicine has not been as positive as expected. Therapies called into question by controlled trials continue to be increasingly used by the practicing physician. Traditional means of disseminating information have not been sufficient. Three specific clinical trials have been examined in this study: the Coronary Drug Project, the Unstable Angina Pectoris Trial, and the Aspirin Myocardial Infarction Study. A new and more effective model for dissemination is expected to result.

Projected Activities: 1978–1982

The NHLBI's Prevention, Education, and Control efforts have evolved from a primary concern with the efficient dissemination of information to an involvement in research on motivation, health behavior, and alternative educational strategies designed to influence health behavior. This process has led to two conclusions: First, there is a continuing need for research designed to find the most effective educational strategies for enabling the public to make more health-oriented decisions; and second, the transfer of information and the promotion of good health behavior are sufficiently urgent that action cannot be delayed until "all the answers are in." What is currently known must be transmitted to the public in the most unequivocal, persistent, and attractive method possible.

Based on these conclusions, the NHLBI has initiated the development and implementation of a comprehensive information and education campaign to inform the public and motivate them to reduce risk factors known to be associated with cardiovascular disease. The mission of this program is to contribute to reductions in morbidity and mortality due to heart, lung, and blood diseases by coordinating a comprehensive risk factor education program. The major current activity is the National High Blood Pressure Education Program instituted in 1972. Potential future program areas include education on smoking, nutrition, diabetes, and other identified risk factors.

The prevention of a number of diseases is dependent on altering the dietary habits of the American people. Investigations are under way at various centers throughout the country on a variety of educational interventions aimed at producing healthier eating habits.

Over the next five years, the goal of this program is to make the American public aware of the relationship between self-imposed risks and disease and aware of feasible and attractive actions to reduce those risks. Development of this campaign will involve a study of the approaches used in advertising and entertainment to influence consumer opinions and decisions as well as concerted efforts to influence the commercial advertising of food processors and fast food promoters. As the campaign continues, joint plans for collaborative efforts will be initiated with related Institutes of NIH, voluntary agencies, professional societies, and other private and government organizations concerned with health promotion.

PROGRAMMATIC PEC ACTIVITIES

Within the three major programmatic areas of the NHLBI—heart and vascular diseases, lung diseases, and blood diseases and blood resources—there are active PEC programs in nine research areas: arteriosclerosis, hypertension, coronary heart disease, congenital heart disease, lung diseases, sickle cell disease, hemophilia, thromboembolic disorders, and blood resources. Notable progress in translating basic knowledge into practical application has been made in several of these areas.

Heart and Vascular Diseases

Since 1972, the NHLBI has placed special emphasis on evaluating programs for prevention and control of hypertension and arteriosclerosis. As a result, a growing body of knowledge exists which, if widely applied, might significantly reduce the death and disability related to these two disorders. Long-range research and demonstration programs have been initiated and enjóy considerable success. In addition, the Institute has developed and imple-

mented PEC programs related to coronary heart disease and congenital heart disease. To provide an in-depth view of the range of activities associated with these PEC programs, only one of these program areas—hypertension—is discussed in detail.

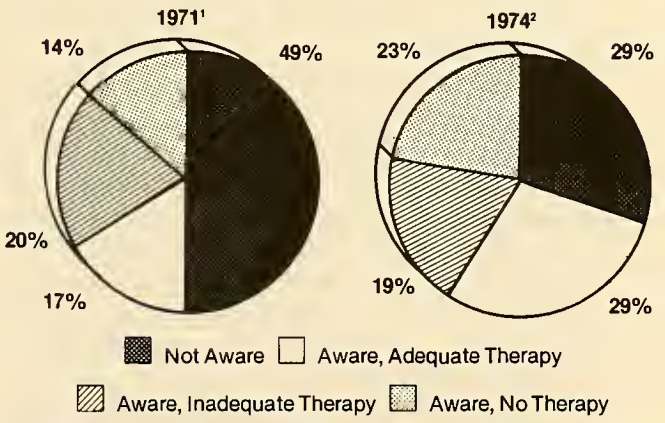
The National High Blood Pressure Education Program represents the Institute's most extensive effort in prevention, education, and control. The success of this effort has tremendous consequences not only for the control of hypertension, but also for increased knowledge and understanding of national programs on any categorical disease or health maintenance issue. The experience of the National High Blood Pressure Education Program is providing new knowledge on how to:

- Initiate a national impetus among health care providers, consumers, and agencies.
- Develop communication channels to specific audiences.
- Assess the need for and mechanisms of consensus-building among primary "actors" related to a health issue, and determine how best to develop that consensus.
- Assess the readiness of specific lay and professional populations to accept and apply new information.
- Identify new data bases necessary to assess the impact of the program.
- Evaluate specific health actions and changes nationwide.
- Determine when major programmatic efforts are needed to effect the changes desired.
- Analyze discrete health behaviors and their determinants.
- Influence media and basic science writers so that their coverage provides appropriate support to achieve program goals.
- Begin to assess the economic implications of the applications of new technologies.
- Demonstrate the implications and pragmatic value of applying behavioral science to solving health problems.
- Initiate a program of national scope, and when sustained Federal effort is no longer necessary, gradually reduce support.

These advances in knowledge place the Institute in a position of increased capability to influence successfully the health of Americans through a national program. The effectiveness of these new skills developed in the National High Blood Pressure Education Program is evident in an examination of some of the trends of the past five years.

- Preliminary data suggest that in 1971 only 50 percent of the 23 million Americans known to have high blood pressure were aware of their condition; by 1974, this figure had risen to 70 percent. Similarly, only 4 million of those hypertensive Americans were under adequate control in 1971; by 1974, that figure had apparently doubled (Figure 8). In addition, there has been a **very marked increase in the number of total patient visits to physicians for hypertension and hypertensive heart disease,** while total patient visits for all causes have increased only slightly.
- **Deaths from hypertension-related cardiovascular disease have declined** at a much sharper rate than those categories of cardiovascular disease not related to hypertension.

Figure 8: HYPERTENSION AWARENESS AND CONTROL



[1]Health and Nutrition Examination Survey, 1971 (Preliminary Data). Computed from unpublished preliminary data furnished by the National Center for Health Statistics.

[2]Survey of 14 Communities, February 1973-June 1974. Hypertension Detection and Follow-up Study, National Heart and Lung Institute.

- **Mortality rates from stroke, hypertensive heart disease, and coronary heart disease are declining** faster in younger age groups than in older age groups.

National trends of this nature are, of course, a result of many factors. However, the striking parallel between the initiation of the National High Blood Pressure Education Program and such marked changes suggests that the program is successful.

Accomplishments: 1972–1978

The National High Blood Pressure Education Program has structured a number of cooperative efforts to control high blood pressure. Specifically, the National High Blood Pressure Education Program:

- **Coordinates the work of more than 150 private, Federal, voluntary, and professional organizations** concerned with some aspect of hypertension prevention, detection, treatment, or control.
- **Established the High Blood Pressure Coordinating Committee,** comprising all major professional organizations and voluntary agencies concerned with high blood pressure control. This committee reviews all program progress and new initiatives and has served as a powerful mechanism for developing a national consensus on issues related to high blood pressure detection, treatment, control, and education.
- Through the High Blood Pressure Coordinating Committee, sponsored the development of the **Joint National Committee Report on the Detection, Evaluation, and Treatment of High Blood Pressure,** a significant step forward in unifying the nation's hypertension control effort. It represents a single national consensus among many major organizations on approaches to detecting, evaluating, and treating hypertension. These organizations include the American College of Cardiology, the American Academy of Family Physicians, the American College of Physicians, the American Heart Association, the American Medical Association, the National Kidney Foundation, the National Medical Association, the Veterans Administration, and the United States Public Health Service. This report has been published in the *Journal of the American Medical Association* and has been widely disseminated to health care providers by the National High Blood Pressure Education Program.
- **Assisted the High Blood Pressure Coordinating Committee in convening the annual National Conference on High Blood Pressure Control.** This conference brings together practitioners and researchers from across the United States to exchange information, ideas, and experiences relevant to upgrading community high blood pressure control programs. In 1977, more than 700 persons attended the conference.
- Through the task force mechanism, **reviewed the adequacy of current physician training in high blood pressure** and formulated models of performance characteristics, learning objectives, and evaluation criteria. These models are now being used by medical schools, testing organizations, and certifying agencies.
- Held a **national conference on hypertension control in the work setting.** Key leaders from business, industry, management, labor, and insurance companies met to discuss the appropriateness of providing education, screening, treatment, and support for therapy maintenance in the work setting. As a result of this conference, the Working Group on Hypertension Control in the Work Setting was established to advise program staff members and review projected activities, and a program on high blood pressure control in the work setting was begun. Members of this group also function as agents of change within their own systems so that opportunities to initiate or expand health services for hypertension control can be exploited.
- Co-sponsored with the Bureau of Community Health Services the **Statewide Hypertension Control Conference.** Representatives from different states discussed model programs for the planning and delivery of statewide high blood pressure control services

and current activities in each state.

- Sponsored a **task force of national nursing organizations** that developed a consensus report on the role of nurses in high blood pressure treatment and control, and co-sponsored with key national professional organizations the **Second National Conference on the Role of the Dental Profession in High Blood Pressure Control.**
- Sponsored development of the **Task Force on Blood Pressure Control in Children.** The final report of this Task Force represents agreement of key professional organizations on detection, treatment levels, and continued care for hypertensive children—an area marked by diversity in medical practice. It was published in the May 1977 issue of *Pediatrics* and is being widely disseminated by the NHBPEP.
- Developed an **annual national mass media educational campaign** in collaboration with the Advertising Council. Radio and television announcements, posters, and print advertisements reach millions of Americans each year with messages about high blood pressure.
- Involved over 121 national organizations and over 1,000 community groups in co-sponsoring an **annual National High Blood Pressure Month.** This activity created a national focus on blood pressure control programs in more than 50,000 hospitals, civic organizations, health departments, voluntary organizations, business and labor groups, and professional societies. As a result, over 1.5 million individuals were screened, referred, and followed-up to assure that they received care. A handbook with suggestions and guidelines and educational materials were prepared by NHBPEP to aid organizations in developing their activities.
- **Provided on-site assessment and technical assistance** in planning and implementing hypertension control programs to community, state, and regional programs. In 1977, more than 75 site-visits were made, and telephone calls for technical assistance averaged more than 90 a month.
- In cooperation with a major drug company, developed **a handbook to aid communities** in creating hypertension control programs. Over 39,000 copies of the handbook have been distributed.
- Established the **High Blood Pressure Information Center,** which answers public inquiries and distributes free educational materials, special reports and studies, posters, radio and television materials, and reprints from professional and lay periodicals. The Center also schedules educational exhibits for both professional and lay group meetings and conventions. The Center provides speakers knowledgeable about high blood pressure or helps organizations find qualified speakers in their own localities. In 1977, more than 2.5 million items were distributed to health care providers, patients, organizations, and the general public. Over 1,700 inquiries were processed each month. An annotated bibliography listing and assessing the merit of all available patient education materials was prepared by the Center in 1977.
- Initiated a series of **national conferences on high blood pressure control for select minorities,** such as Native Americans, Asian-Pacific Americans, Cuban-Americans, Mexican-Americans, Afro-Americans, and Puerto Rican-Americans. These conferences all conclude with a series of recommendations that are submitted to an ad hoc committee on hypertension in minority populations, which advises the National High Blood Pressure Education Program on the special needs and interests of minorities.
- Sponsored the **National Board of Medical Examiners Hypertension Medical Audit,** which will be completed in the spring of 1978. This project will help physicians in private practice audit the quality of hypertension care they provide and compare their approach with nationally recognized guidelines.
- Co-sponsored a task force to develop **curriculum guidelines for training of physicians in patient education.** This effort also involves the Bureau of Health Manpower, the Amer-

ican Academy of Family Practice, and the Society of Teachers of Family Medicine. It represents the first cooperative program of its kind in patient education and should prove instrumental in developing national standards and guidelines.

- Funded 11 **educational research projects** aimed at exploring innovative and cost-effective methods to achieve a greater degree of control of blood pressure in hypertensives. Patient education is the primary tool. This program is supporting behavioral research in health education, attitudes, motivation, and compliance as they relate to the control and treatment of hypertension.

Through programs such as these, significant progress has been made in public and professional awareness of high blood pressure and in the numbers of individuals initiating therapy. Nevertheless, achieving control and maintaining individuals on therapy both continue to present a challenge. Treatment for hypertension is lifelong, must be tailored to the individual, and may be accompanied by undesirable side effects. Therefore, it will remain a challenge to establish and maintain the behaviors necessary to sustain such therapy over years.

Three program initiatives have been taken to explore new ways to meet that challenge: high blood pressure control programs in the work setting, statewide high blood pressure coordination programs, and pilot studies of model community high blood pressure control programs within populations having a high prevalence of this disorder. The work setting program is demonstrating education and control capabilities and collecting relevant information on the costs of employee health programs in private industry. The state programs are coordinating statewide high blood pressure control activities, including evaluations of their impact on morbidity and mortality rates. The pilot studies project is evaluating models of community high blood pressure control in selected areas. This will involve developing methodology for evaluating community organization, cost-effectiveness of management systems in the community setting, and the comparative effectiveness of high blood pressure therapy in public and private clinics. Such programs will also examine ways in which nurses, pharmacists, and other health care professionals can assist in providing long-term follow-up for persons on antihypertensive therapy.

The above activities are only highlights of the extensive educational research and demonstration programs conducted by NHLBI with a special focus on high blood pressure. These activities have all been designed so that, ultimately, local, state, and regional organizations and agencies can continue the work of the National High Blood Pressure Education Program without intensive Federal assistance.

Projected Activities: 1978–1982

In the next five years, efforts to control high blood pressure will continue to receive major programmatic emphasis. Among specific Institute initiatives are the following:

- Continuation of the National High Blood Pressure Education Program to inform, educate, and demonstrate the value of detecting and treating hypertension in asymptomatic persons. Special emphasis will be placed on enhancing patient compliance with therapeutic regimens.
- Continuation of educational research programs to develop new methods of increasing awareness of hypertension, promote patient education, and provide improved methods of assuring patient adherence to treatment.
- Continuation of the Hypertension Detection and Follow-up Program (HDFP), which is studying the effectiveness of antihypertensive therapy to reduce morbidity and mortality from hypertensive heart disease. This community level trial is aimed at control of high blood pressure in patients with mild, moderate, and severe elevations of blood pressure.
- Continuation of demonstration programs:
  - Work setting high blood pressure control programs to demonstrate education and control capabilities and to collect relevant cost information regarding employee health programs in private industry.
  - Development of a long-term, collaborative program to train Blue Cross account executives to provide their clients with consultation on planning and implementing high

blood pressure control programs at the worksite.

- Continuation of state high blood pressure coordination programs designed to coordinate high blood pressure control programs on a statewide level.
- Pilot studies of community high blood pressure control programs within populations having a high prevalence of hypertension in order to evaluate the cost-effectiveness of management systems in the community setting.

- Wide dissemination of medical guidelines for the detection, evaluation, and treatment of high blood pressure. These guidelines represent a national consensus of the major professional and voluntary organizations concerned with the treatment of hypertension. Every effort will be made to promote the use of these standards by medical practitioners.
- Identification of barriers to high blood pressure control in the medical care delivery system and education of health care administrators to promote reduction of those barriers.
- Assistance at all levels of health care delivery system in order to improve the quantity and quality of patient education and counseling concerning hypertension.
- Promotion of the use of ancillary health professionals in high blood pressure control programs.
- Wide dissemination of the *Task Force Report on Blood Pressure in Children,* which clearly delineates the importance of, and methods for, monitoring children's blood pressure yearly. The charts developed for evaluating children's blood pressure will be widely distributed to practicing physicians.
- Evaluation of the effectiveness of the national effort to improve the control of high blood pressure through a national survey of public knowledge, attitudes, and practices related to high blood pressure. This survey, a follow-up to the Harris Survey conducted in 1972, will allow the Institute to compare knowledge and attitudes before and after the initiation of the NHBPEP.

Schedule

The NHBPEP will continue as a major program emphasis throughout the next five years. The HDFP is expected to complete its five years of treatment and follow-up of the 11,900 hypertensives enrolled in the program in fiscal year 1980. Data analysis will continue through fiscal year 1982.

Demonstration programs in the work setting, begun in fiscal year 1977, will continue until fiscal year 1980.

Community demonstrations and statewide model programs, initiated in fiscal year 1977, will continue through fiscal year 1982.

Dissemination of the medical guidelines, efforts to reduce system barriers to hypertension control, promotion of expanded roles for ancillary health professionals, and assistance in developing more effective patient education strategies will continue throughout the next five years as an integral part of the NHBPEP.

Evaluation of the impact of the NHBPEP through a national survey will begin in fiscal year 1978.

Lung Diseases

Pulmonary research has contributed to better understanding of the causes of respiratory diseases and the processes that underlie their development, to more precise and earlier detection of abnormalities associated with these disorders, and to improvements in therapy. However, the findings of such research can have only minimal impact on national health unless there is an informational link between those who perform the research and those who practice medicine in the community. Moreover, if individuals are to participate in maintaining their own health, they must be informed about the types of behavior and life styles that contribute to good health and about the known factors that can cause or contribute to disease.

For these reasons, the NHLBI has mounted a significant effort directed toward initiating and improving methods to facilitate the transfer of knowledge about the lung and lung diseases from the research setting into clinical practice through educational measures, demonstrations, and control programs.

Accomplishments: 1972–1977

Lack of a comprehensive plan in the past slowed the development of an education program for prevention and control of respiratory diseases. In spite of this, however, significant initial steps have been taken since the legislative mandate of 1972. During this time, the NHLBI has:

- **Established a National Research and Demonstration Center at the University of Vermont** to facilitate and expedite translation of basic research findings to practical patient care in local communities. The Center coordinates the activities of several groups, including the State Department of Health, the Vermont Lung Association, and members of the Departments of Community Medicine, Continuing Medical Education, Medicine, Pathology, and Physiology of the University of Vermont School of Medicine. Goals and activities of this Research and Demonstration Center include:
  - Investigation of *occupational lung diseases* such as silicosis and farmer's lung, emphasizing epidemiology, prevention, and control in defined populations. Educational programs have been instituted to alert farmers to the hazards of inhaling dusts that result in farmer's lung and to urge them to take preventive steps to keep from breathing the materials.
  - *A computer-assisted preoperative evaluation project* that defines the risks and appropriate interventions for persons with respiratory disease who require surgery.
  - Development of a *statewide network for surveillance, diagnosis, treatment, and control* of tuberculosis, pneumonia, industry-related lung diseases, and other pulmonary disorders in ambulatory patients.
  - Development of a program for providing *regional assistance in the management of respiratory diseases,* employing an inter-hospital computer network for information storage and retrieval, data interpretation and analysis, aid in diagnosis and treatment, and the dissemination of new knowledge.
  - Development of a *computerized progressive care program* oriented to the clinical management of respiratory diseases, including technical assistance, quality control, and evaluation of new programs within community hospitals.
  - *Dissemination of new knowledge* via a television network linking seven medical care facilities and two university medical centers.
  - *Promotion of pulmonary health through a school health demonstration program* which addresses not only factual information but also attitudes and values.
  - Development of a *breathing workshop program,* a patient education program employing self-instructional and audio-visual techniques to improve patient skills, understanding of their disease, and adherence to therapy and control measures.
  - Development of a *regional public information system on respiratory diseases* in collaboration with the Vermont Lung Association and the State Department of Health.

  The cooperative activities at the Vermont Lung Center indicate that it is possible to develop a prevention, education, and control program that draws upon many segments of professional communities and reaches a variety of target groups.
- Funded, at three institutions, the development of **educational programs concerned with early treatment of acute respiratory insufficiency in adults.** These institutions plan an outreach program for more than 40 area hospitals. The program is aimed at physicians who have no special training in respiratory disease and at nonphysician health professionals who are likely to have first contact with patients suffering from acute respiratory insufficiency. Both innovative and well-established educational methodologies are being employed. Three different approaches to information dissemination are being tested to assess their relative effectiveness.
- Funded the development of five educational

programs in the **recognition and treatment of acute respiratory distress in infants,** the most common cause of newborn deaths. Death may be prevented if respiratory insufficiency is anticipated or recognized as soon as it begins and therapeutic measures instituted promptly. The educational programs are aimed at physicians, nurses, physician's assistants, midwives, and other professionals involved in prenatal care, delivery, and neonatal care. All are being taught to recognize respiratory distress and initiate early treatment.

- Developed programs to **design and evaluate continuing education programs in pulmonary medicine.** This new initiative focuses on two major problems: motivating practicing physicians who lack specialty training in pulmonary medicine to seek and use continuing education resources in this field; and evaluating procedures for assessing the impact of continuing medical education on the quality of care of patients with pulmonary disease.
- Initiated the development of a new series of **patient education programs for childhood asthma.** These programs are aimed at developing effective methods to teach asthmatic children and their parents to cope more effectively with the disease. An improved understanding of the factors causing bronchospasm and the actions to take when it occurs could result in less restricted activity for the child, a lessening of the accompanying psychological effects on child development, and a significant reduction in the need for emergency care.
- **Developed measurement techniques to screen asymptomatic individuals with early interstitial lung diseases.** Preliminary studies have shown that the course of such diseases can be altered by removing the slightly impaired worker from the polluted environment.
- Supported the development of on-line computer based systems for **managing labor and delivery and of a comprehensive** perinatal and postnatal data base relative to neonatal respiratory distress syndrome (hyaline membrane disease). Ultimately, a scoring system will be developed as a basis for the initiation of therapeutic procedures that assure optimal outcome in a given case of respiratory distress syndrome.

Application of the behavioral and social sciences to influence the prevention and control of lung diseases is now gaining momentum. In 1976, the NHLBI convened the Task Force on Respiratory Diseases: Prevention, Control, and Education. The Task Force and its task groups included experts from pulmonary, industrial, and community medicine; epidemiology; health professional and public health education; behavioral science; economics; and communications. The report of the Task Force examines the state of the art in prevention and control of respiratory diseases, recommends areas where immediate application of existing knowledge lends itself to professional and public education and demonstration programs, and identifies areas that require further research and testing. This report establishes much needed priorities for the translation of biomedical research and knowledge into prevention and control of respiratory diseases and will serve as the basic program plan for the next 10 years.

The Task Force report concludes that a significant impact on prevention and control of respiratory diseases can be made by careful analysis of the most critical intervention points, determination of the most effective strategies for prevention, control, and rehabilitation, and step-wise development of a cohesive and well-designed program. With the guidelines provided by the Task Force panel of experts and the experience of the past five years, it is now possible to develop this program in such a way that notable progress may be expected in the coming years.

Projected Activities: 1978–1982

Education, demonstration, and control programs will be initiated during the next five years to facilitate the transfer of basic knowledge to clinical practice. Professional education will be an integral part of the program. Scientists will be trained for careers in pulmonary research, and practicing physicians will receive continuing education to improve

their competency in pulmonary medicine. The following key initiatives, recommended by the Task Force on Prevention, Control, and Education, are among those which the NHLBI will implement during the next five years:

- Develop educational programs for physicians, other health professionals, and the public to increase utilization of information about the causes and symptoms of chronic bronchitis and emphysema.
- Develop information dissemination and education programs for individuals, communities, and health professionals to discourage cigarette smoking among teenagers and those at high risk of chronic obstructive lung disease, and to facilitate the development of effective community non-smoking programs.
- Develop educational programs for physicians to prevent hyaline membrane disease by prenatal assessment of lung maturity before elective delivery or Caesarian section, and insure early treatment of hyaline membrane disease by the assessment of lung maturity in all premature births.
- Improve prevention and prompt diagnosis of chronic obstructive lung diseases by developing programs to increase the responsiveness of health professionals and the public to the importance of risk factors and early symptoms..
- Increase the capability of community hospitals to diagnose and rapidly treat acute respiratory failure associated with chronic obstructive lung disease.
- Develop programs to educate health professionals and the public about the characteristics of early cystic fibrosis, the risks of delayed therapy, and resources available for diagnosis and effective treatment.
- Improve the control of asthma through programs that increase the ability of health professionals to diagnose and treat asthma through educational programs to improve their knowledge and skills, and increase the ability of patients to participate in the management of their own disease.
- Develop information and education programs to increase early diagnostic assessment of lung injury and rapid therapeutic intervention designed to reduce the incidence of progressive, diffuse, interstitial fibrosis; improve health professionals' understanding and recognition of pulmonary manifestations of such systemic disorders as sarcoidosis and connective tissue diseases; and stimulate appropriate action among health care providers to reduce potential pulmonary complications associated with many types of drug therapy.
- Improve the control of pulmonary fibrotic diseases through programs that increase active patient participation in long-term therapy.
- Develop and evaluate programs to make individuals, communities, industries, and health professionals more aware of environmental risk factors and of the means to reduce or eliminate them; and establish a clearinghouse to receive and disseminate information about environmental risks to the lungs.
- Develop and promote methods to provide workers with measurements of their personal levels of exposure to occupational hazards.
- Promote the use of pulmonary function tests in routine examinations of individuals at high risk of respiratory disease.
- Develop high quality educational programs in pulmonary medicine in the nation's medical schools through the Pulmonary Academic Award Program and the National Pulmonary Faculty Training Program.

Schedule

This wide range of prevention, control, and educational activities will form the basis for the Division's program development during the next five years. In fiscal year 1978, opportunities will be assessed and priorities established; from fiscal year 1978 to fiscal year 1982, programs will be developed and implemented at successive stages.

Blood Diseases and Blood Resources

The NHLBI is supporting demonstration projects in the areas of blood diseases and resources which bridge the gap between the validation of new research findings and their broad implementation in the health care arena. Currently, prevention, education, and control activities related to sickle cell anemia, hemophilia, thromboembolic disorders, and blood resources are under way. The Institute is currently developing plans for a comprehensive program of education, screening, and counseling related to Cooley's anemia. To provide an in-depth view of the range of activities associated with these prevention, education, and control programs, only one of these program areas—sickle cell disease—is discussed in detail.

Despite current research in and clinical knowledge of sickle cell anemia, the general public, patients, and carriers of this hereditary disease do not have an adequate understanding of the disorder and its significance. Health care providers, community health programs, educators, insurance companies, and employers also need the latest information to improve the clinical care and education of sickle cell disease patients and their families and to lessen the negative psychosocial impact of the disease. Effective public screening and genetic counseling present the option of preventing increased incidence of the disease.

In 1972, no systematic approach to screening and counseling existed. Consequently, the National Sickle Cell Disease Program was established to provide an aggressive and innovative professional and public education program, disseminate information, initiate and expand participation of communities in screening and counseling activities, and contribute to improved clinical care of all patients. The challenges of such a mission were only partially understood in 1972. Although the activities of the past five years have brought about significant progress toward these goals, the program has still managed to reach only a segment of the population.

Accomplishments: 1972–1977

Since its initiation, the program has:

- **Coordinated the National Sickle Cell Disease Program,** a major collaborative effort to accelerate research on sickle cell disease, and improve its diagnosis, control, and treatment. This program established Comprehensive Sickle Cell Centers, Sickle Cell Screening and Education Clinics, a mission-oriented research and development program, biomedical research, a public and professional education program, and a hemoglobinopathy (red blood cell disorders) training program.
- Through the 24 Sickle Cell Screening and Education Clinics (administered by the Bureau of Community Health Services in the Health Services Administration), **screened and counseled over 600,000 individuals** and distributed information to more than 4 million Americans. These clinics have developed diverse counseling protocols to assure content accuracy and uniformity. Now published, these protocols will serve as models for non-Federal programs that provide sickle cell services.
- Established 15 **Comprehensive Sickle Cell Centers** throughout the country. These Centers, which combine activities in research, education, and counseling with community outreach, have proved to be an effective model that embraces the needs, opinions, and participation of the client population and a positive interaction with the academic and scientific communities. The education programs use a wide range of specialized educational materials, exhibits, seminars, and lectures directed toward increasing the awareness and knowledge of the general public, high school students, medical students, interns, residents, and practicing physicians about sickle cell trait and disease, with special attention on socioeconomic and ethical considerations. Tutorial programs for students with sickle cell anemia, initiated by the Centers, have helped to decrease school absenteeism, increase scholastic achievement, and decrease the psychological pressures of adaptation, and have led to an overall increase in self-esteem. For the adult patient, vocational rehabilitation is provided through individual career counseling.

Genetic diseases require considerable personal adjustment fo the concerned individual. For this reason, counseling is an im portant component of all sickle cell programs.

- Provided a multitude of **educational service activities** including evaluation of sickle cell films, brochures, and pamphlets; participation in workshops, conferences, and symposia; compilation of research articles; exhibits at conventions and conferences; responding to inquiries and requests for information; developing a directory of sickle cell programs; providing technical assistance t community programs; and coordinating edu cation and information programs across Fed eral agencies.

- Established a collaborative program wit three non-governmental organizations t carry out **programs in public awareness,** t

aid in the dissemination of factual information, and to conduct educational programs in sickle cell anemia throughout the country. This program is aimed at health providers, employers, insurance companies, health educators, and persons who have sickle cell anemia or sickle cell trait.

- Held 10 **regional sickle cell education workshops** during 1976 in selected key cities in the United States to provide training and educational activities to more than 600 people. As a result of these workshops, an 18-hour curriculum on sickle cell education has been developed.
- Produced a **self-instructional sickle cell audiovisual kit for physicians** to assist in educating them via cassette, film strip, and manual about the history, symptoms, and physiological and psychological problems related to sickle cell anemia and sickle cell trait. The kit was disseminated to 6,000 physicians.
- Developed **model agencies focusing on sickle cell disease** in selected communities to determine needs and methods for reaching people. Established in rural, suburban, and urban areas, the agencies used all forms of media and modes of operation to generate interest in sickle cell disease.
- Established a permanent **exhibit on sickle cell disease in the health sciences section of the Chicago Museum of Science and Industry.** This inclusive exhibit portrays many aspects of sickle cell disease, including the molecular characteristics, evolution of scientific knowledge, origin and distribution of the HbS gene, symptomatology, and mechanisms of genetic transmission.
- **Demonstrated accurate diagnostic techniques** for both routine screening and advanced methods for identifying hemoglobinopathies. Federal programs are monitored for quality control through a proficiency testing program that has resulted in accurate definitive diagnoses. The Institute has coordinated educational efforts with other Federal agencies and has developed collaborative training programs for laboratory personnel.
- Held the **First National Sickle Cell Educational Symposium** (May 1976) to present current clinical, scientific, and educational information to physicians, paramedical personnel, health educators, and health workers in the field of sickle cell disease. The proceedings of this symposium have been published and widely disseminated.
- Conducted clinical research activities, including an **evaluation of emergency room procedures for patients experiencing sickle cell crises** or other complications. Because complications are often not recognized or are sometimes misdiagnosed, a protocol has been developed that highlights the symptoms and discusses various diagnosis and treatment procedures. Use of the protocol has improved emergency room care in a test hospital. The protocol is now being made available to other medical centers throughout the country.

Despite the above efforts, only a small segment of the population has been reached through the existing network of screening, education, and counseling programs. Clearly, there is need for innovative programs that reach a wider segment of population than just those at risk.

Projected Activities: 1978–1982

An intensified effort will be made to educate a larger percentage of health professionals and the population at risk and to develop more effective educational and counseling programs during the next five years. The program plans to:

- Evaluate the effect of **sickle cell counseling** on both the acquisition and retention of knowledge and also on the feelings, attitudes, and behavior of persons receiving counseling. A prospective experimental design study will be created for this purpose.
- Evaluate the impact of the **psychosocial aspects** of sickle cell disease on patients and their families and the influence these aspects have on the quality of life of sickle cell patients.

- Develop and evaluate modalities for providing education on sickle cell trait and disease during medical school, internship, and residency training programs.
- Develop and evaluate methodologies for providing **continuing education** on sickle cell trait and disease to practicing physicians.
- Disseminate up-to-date information to emergency rooms across the country to upgrade the *management of sickle cell patients in crisis.*
- Develop collaborative efforts with other regional and community health agencies for educating the family about sickle cell disease.
- Establish telephone "hotlines" for *sickle cell information* in communities with a high concentration of "at-risk" populations.
- Design *curricula* for teaching sickle cell and other genetic diseases to high school and college students.
- Develop a mechanism for conducting ongoing *evaluation of the health education components* of sickle cell programs.

Schedule

The prospective study to evaluate the effectiveness of sickle cell counseling will be initiated in fiscal year 1978 and completed by fiscal year 1980. Methodologies for continuing education, medical school education, and emergency room education are ongoing and will continue through fiscal year 1982.

6. RESOURCES: THE LIMITING FACTOR

INCREASING MANDATES

As a result of increases in NHLBI mandates in 1972 and 1976, new programs in heart, lung, and blood diseases and in blood resources, have been promulgated and existing programs expanded in scope. Consequently, the Institute's professional scientific community has grown greatly in size and fields of interest. In response to these mandates, the diversity, complexity, and number of research projects proposed by this broadened constituency have increased dramatically.

Over the past five years, the program planning functions of the Institute have monitored this large growth of opportunity and need, and have noted the Institute's inability to keep pace with this growth. Yet it is not for want of ideas or commitment that the NHLBI is unable to keep pace with advances in knowledge which are rapidly evolving as a result of the Institute's activities. This report attests to the significant progress that has been made under the National Program. However, as we outline in this chapter, the availability of sufficient resources and professional staff is limiting the full implementation of the National Program.

RESOURCES: INCREASING DEMAND

To properly implement the newly mandated programs planned as a result of the 1972 Act and its subsequent renewal, the "buying power" of the Institute must parallel inflationary pressures as well as advances in sophistication made in scientific methodology. As shown in Table 4, the Institute's obligations for fiscal year 1971, the last year prior

Table 4

NHLBI OBLIGATION SUMMARY FOR 1971-1977 IN CURRENT AND CONSTANT DOLLARS (Dollars in Millions)

Year	Current $	% Increase[1]	Constant $[2]	% Increase[1]	Legislative Landmarks
1971	194.8	0	194.8	0	
1972	232.6	19.4	221.5	13.7	PL 92-423
1973	255.7	31.3	232.7	19.5	
1974	327.3	68.0	278.3	42.9	
1975	327.9	68.3	250.1	28.4	
1976	368.6	89.2	261.6	34.3	PL 94-278
1977	396.9	103.7	262.9	35.0	

[1]Compared to base year (1971).

[2]This table uses inflation factors derived by Dr. Herbert Woolley, NIH, September, 1975. These factors are: 1972 = 1.050; 1973 = 1.099; 1974 = 1.176; 1975 = 1.311; 1976 = 1.409; 1977 = 1.510.

to the passage of the National Heart, Blood Vessel, Lung, and Blood Acts, were $194.8 million. By fiscal year 1977, the current dollar level had risen to $396.7 million, an increase of $201.9 million.

However, by calculating obligations in "constant dollars"—which takes into account the inflationary spiral of the last five years—the "buying power" of the Institute to implement its programs is considerably reduced (Table 4). In constant dollars, the Institute's 1977 obligations were $262.7 million, an increase of $67.9 million over the 1971 level. The NHLBI actually had greater "buying power" in fiscal year 1974 than in fiscal year 1977: In 1974, the Institute's $329.5 million obligations were equivalent to $280.2 million in constant dollars, whereas the $396.7 million obligations in fiscal year 1977 are equivalent to only $262.7 million in constant dollars. To state it another way, the Institute's purchasing power decreased 8.9 percent between 1974 and 1977 even though new mandates were added in 1976. When the budgets for the individual categories of research in heart, lung, and blood are converted to constant dollars, the "buying power" for each of the categories is also lower in FY 1977 than it was in FY 1974: down 10.6 percent for heart, 6.3 percent for lung, and 5.3 percent for blood.

The National Heart, Lung, and Blood Institute's budget has accounted for 16 to 17 percent of the NIH budget during the last 10 years—both prior to, and after, the Institute was given the mandates for lung and blood diseases research (Table 5). A fiscal constraint is evident when one looks at the budget for the Institute's largest Division, the Division of Heart and Vascular Diseases, which manages two-thirds of the Institute's extramural program. In 1971, the Division's budget was 10.5 percent of the NIH budget, while it decreased to 9.3 percent in 1977. During the same period, the Institute initiated several large heart disease-related programs designed to validate and translate research into health benefits for the nation. These included several large multi-center collaborative clinical trials related to the prevention, detection, and/or treatment of arteriosclerosis, hypertension, and coronary heart disease; Specialized Centers of Research on arteriosclerosis, hypertension, and ischemic heart disease; a National Research and Demonstration Center on cardiovascular disease; and a comprehensive national program of education and education research on hypertension.

Another indication of the growing pressure on the Institute's limited resources is the steady increase in the number of research grant applications submitted and subsequently reviewed by the NHLBI (Table 6). The resources requested to carry out the research proposed in these applications increased significantly (Table 7): In 1971, $59.7 million in di-

Table 5

NIH RESEARCH SUPPORT, FISCAL YEARS 1971-1977
(Dollars in Millions)[1]

	1971		1972		1973		1974[2]		1975[2]		1976[3,6]		1977	
Organization	$	%	$	%	$	%	$	%	$	%	$	%	$	%
Total NIH[4]	1,181	100.0	1,466	100.0	1,484	100.0	1,947	100.0	2,044	100.0	2,186	100.0	2,425	100.0
NHLBI[5]	195	17.0	233	16.0	256	17.0	327	17.0	328	16.0	369	17.0	397	16.0
DHVD	124	10.5	139	9.5	147	9.9	192	9.9	189	9.2	215	9.8	227	9.3
DLD	16	1.4	23	1.6	28	1.8	45	2.3	45	2.2	51	2.3	55	2.3
DBDR	20	1.7	32	2.2	40	2.7	51	2.6	51	2.4	53	2.4	57	2.4

[1]Current Dollars.
[2]Includes release of impounded FY 1973 funds.
[3]Excludes transition quarter.
[4]Excludes National Library of Medicine, Buildings and Facilities, and Office of the Director, NIH.
[5]NHLBI budget includes Division of Heart and Vascular Diseases (DHVD), Division of Lung Diseases (DLD), Division of Blood Diseases and Resources (DBDR), as well as direct operations, program management, and intramural research.
[6]$3.5 million Biomaterials Program transferred from DBDR to DHVD.

Table 6

TRENDS IN NHLBI INVESTIGATOR-INITIATED RESEARCH: REGULAR RESEARCH AND PROGRAM PROJECTS[1]

Number of Grants (New and Competing Renewals)				
Year	Reviewed	Approved	Awarded	% Approved Awarded
1971	1,142	738	444	60
1972	1,196	788	494	63
1973	1,288	915	427	47
1974	1,528	1,130	620	55
1975	1,515	1,123	614	55
1976	1,585	1,155	666	58
1977	1,999	1,441	660	46

[1]New and renewal applications.

Table 7

TRENDS IN NHLBI INVESTIGATOR-INITIATED RESEARCH: REGULAR RESEARCH AND PROGRAM PROJECTS

FUNDING[1] (Direct Costs Only[2])

Millions of Dollars				
Year	Requested	Approved	Awarded	% Approved Awarded
1971	59.7	30.1	18.2	60
1972	71.2	36.9	26.0	70
1973	77.7	43.0	25.2	59
1974	112.1	54.7	41.1	75
1975	114.5	56.7	33.4	59
1976	119.7	61.9	38.8	63
1977	181.9	91.3	49.8	55

[1]New and renewal applications.
[2]To estimate total costs, multiply direct costs by 1.32 (factor derived from 1977 new and competing investigator-initiated grant awards).

rect costs were requested from the Institute; in 1977, the figure had more than tripled, to $181.9 million.

In addition to the dramatic increase in the direct costs requested—a reflection of the increased sophistication of science as well as of inflation—the indirect costs which accompany each award also have risen steadily. Table 8 shows for a specific portion of the Institute's grant-supported activities over the period 1970–1977 the direct costs, indirect costs, indirect costs as a percentage of direct costs, and total cost of research (direct costs plus indirect costs).

Over the last five years, the commitment base of ongoing research—i.e., the subsequent years' costs of resources committed to previously funded research programs—has steadily increased.

These factors, considered together, account for the large number of *approved* research grant applications which the NHLBI cannot now support. The increasing commitment base; the increase, especially in the last year, in the number of grant applications being submitted to, and reviewed by, the NHLBI (Table 6); the 50 percent increase in direct costs requested by community-based investigators in the last year (Table 7)—a threefold increase in direct costs requested and approved during the period 1971–1977; and the steadily climbing indirect cost rates (Table 8) all mean that the NHLBI is faced with an inability to fund high priority investigator-initiated programs.

Table 8

GROWTH OF INDIRECT COST RATES OF RESEARCH GRANTS,[1] FISCAL YEARS 1970-1977

Fiscal Year	Direct Cost	Indirect Cost	Indirect Cost as a Percent of Direct Cost	Total Cost
1970	$ 68,466,617	$17,986,387	26.3	$ 86,453,004
1971	72,020,575	20,021,425	27.8	92,042,000
1972	81,350,199	25,035,497	30.8	106,385,696
1973	86,539,991	27,674,325	32.0	114,214,316
1974	109,691,890	37,797,863	34.5	147,489,753
1975	101,970,760	36,288,184	35.6	138,258,944
1976	124,915,900	44,436,926	35.6	169,352,826
1977	142.110.745	51.021.715	35.9	193,132,460

[1]Includes Research Project Grants, Program Project Grants, and Sickle Cell Centers.

INSTITUTE STAFF

The growth of the Institute's mandates and of the programs designed to fulfill those mandates has placed increasing responsibilities on the NHLBI staff for program development, initiation, implementation, management, and evaluation. In spite of this significant growth in work load, there were only small increases in the number of staff members between 1972 and 1976, and a *decrease* in 1977 (Table 9 and Figure 9). This decrease has presented a problem in light of the sharp increase in the number of research grant applications submitted, reviewed, and approved (Table 6).

THE CHALLENGE AHEAD

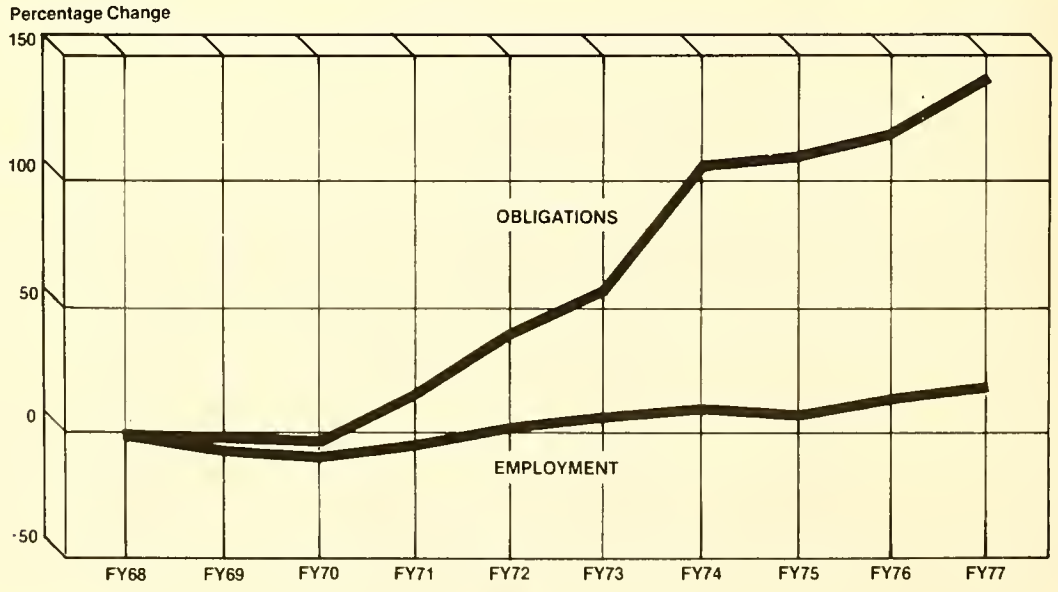
Clearly, if the NHLBI is to continue its record of achievement toward the ambitious goals established for the next five years by implementing the important research program activities described in this report, additional resources and staff positions well beyond those currently projected will be required. At a time when years of research are beginning to pay off in terms of improved understanding of disease etiology, pathogenesis, and risk factors, as well as in terms of modest decreases in morbidity and mortality associated with cardiovascular diseases, and at a time when the future holds promise of even greater progress toward the ultimate goal of disease prevention, it is critical that the momentum of progression along the research spectrum not be lost due to the lack of sufficient resources and staff.

Table 9

COMPARISON OF TRENDS IN NHLBI FULL-TIME PERSONNEL

Year	Obligations	No. Employees	Comments
1972	232.6	618	P.L. 92-423 increased the Institute's mandates and responsibilities.
1973	255.7	647	
1974	327.3	692	
1975	328.0	691	
1976	368.6	749	P.L. 94-278 increased the Institute's mandates and responsibilities.
1977	396.9	723	Personnel ceiling frozen at this level.

Figure 9: NHLBI OBLIGATIONS AND EMPLOYMENT: FUNDS AND PERSONNEL CHANGE FROM 1968 BASE



PROJECTED RESOURCE NEEDS

To maintain the momentum of the National Program, the NHLBI continually reviews the state of the art of its various research programs, projects future progress, plans new initiatives, and estimates resource needs. Thus, the Institute's resource projections and allocations are based on scientific and professional judgment as to the resources—fiscal, manpower, facilities, and time—required to assure program continuity and to accomplish the objectives of the National Program.

The resource allocations presented in Table 10 are consistent with the program activities projected in this report. These allocations have been distributed in such a way as to build on past accomplishments and to anticipate future opportunities. In accordance with the legislation, at least 15 percent of the fiscal resources are projected for diseases of the lung and at least 15 percent toward the problems of blood diseases and blood resources.

The fiscal requirements for the National Program total approximately $598 million in fiscal year 1979. These requirements increase incrementally to $678 million in fiscal year 1983. The financial resources being sought for full implementation of the National Program represent a substantial increment over current resources. With the exception of resources projected for manpower, however, the revised resource estimates in this report represent minor modifications or changes in timing from those projected a year ago.

The rationale for the resource projections for the programs in the Five-Year Plan is delineated below. (More detail is provided in Chapters 3 and 4.)

- **Investigator-Initiated Research Programs.** To maintain a strong and productive investigator-initiated research program within the resources available, the Institute has had to severely encroach upon other areas of importance to the success of the National Program. It is of great concern to the NHLBI that there has been a large increase in the number and cost of research grant applications received without a concomitant increase in funds available to support a large percentage of approved applications. The budget in Table 10 allows for funds to meet the increasing research needs.
- **National Research and Demonstration Centers.** These Centers will provide an important mechanism by which the Institute can ensure that the advances gained through research are validated and translated expeditiously to im-

Table 10

PROJECTED RESOURCE ALLOCATION[1] FOR THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM, FISCAL YEARS 1979-1983
(Dollars in Millions)

	1979	1980	1981	1982	1983
Extramural Research Programs					
Heart and Vascular Diseases	243.4	249.0	252.0	258.0	261.0
Lung Diseases	59.5	62.0	63.6	66.3	68.5
Blood Diseases and Resources	65.0	67.6	69.9	73.3	75.5
National Research and Demonstration Centers	40.0	43.0	45.5	71.5	73.3
Prevention, Education, and Control Programs	38.2	39.8	42.9	49.0	55.0
Training	38.8	40.0	45.0	48.0	51.3
Construction	35.0	35.0	35.0	0	0
Intramural Research	42.9	43.9	45.6	46.8	48.5
Direct Operations and Program Management	37.0	38.0	40.0	43.0	44.9
Total	599.8	618.3	639.5	655.9	678.0

[1]These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

proved health care in the community. The projected budget provides for an expanded program in 1982.

- **Prevention, Education, and Control Programs.** To provide physicians, related health personnel, and the public with the most up-to-date information in the areas of cardiovascular, pulmonary, and blood diseases, initiation and coordination of efforts with voluntary, professional, and civic organizations have been a major function.
- **Construction.** It its 1976 annual report, the National Heart, Lung, and Blood Advisory Council stressed the high priority on the construction of research facilities for the National Program. Construction of appropriate and adequate facilities is important for the planned increase in program activity.
- **Training.** An increment of resources available for manpower is dictated by the needs of the long-range research, education, and demonstration programs of the Institute detailed above.
- **Intramural Research.** Slight increases in the intramural research program from 1981 through 1983 reflect the operation of the proposed Ambulatory Care Facility.

An alternate, lowerbound budget resource allocation plan is presented in Table 11. This plan would delay, for one year, the funding of Institute-solicited research programs—i.e., research grants and contracts in areas of opportunity identified by the NHLBI. It would defer the funding of additional centers and limit the number of new centers. The prevention, education, and control programs would undergo only modest increases. Funds for construction would be eliminated, the budget for training would be reduced, and there would be modest decreases in the intramural research program. The research management and program services budget would be adjusted accordingly.

Table 11

PROJECTED LOWERBOUND RESOURCE ALLOCATION[1] FOR THE NATIONAL HEART, BLOOD VESSEL, LUNG, AND BLOOD PROGRAM, FISCAL YEARS 1979-1983
(Dollars in Millions)

	1979	1980	1981	1982	1983
Extramural Research Programs					
Heart and Vascular Diseases	241.0	247.8	249.6	251.2	255.3
Lung Diseases	57.3	60.4	63.5	64.5	67.6
Blood Diseases and Resources	63.2	67.8	69.1	70.2	73.2
National Research and Demonstration Centers	14.1	18.0	19.8	20.6	23.0
Prevention, Education, and Control Programs	33.0	38.0	40.9	42.4	44.8
Training	35.0	35.4	36.8	38.9	41.3
Construction	0	0	0	0	0
Intramural Research	40.9	41.5	43.0	44.0	45.5
Direct Operations and Program Management	36.0	38.6	40.5	41.5	42.9
Total	520.5	547.5	563.2	573.3	593.6

[1]These tabulations give the general primary thrust of activities, even though these activities generally involve more than one subprogram.

7. LEGISLATION, PLANNING, EVALUATION, AND COORDINATION

With the passage of Public Law 92-423 in 1972, Congress (1) mandated that the NHLBI develop a plan for a comprehensive National Program of research, prevention, education, and control activities related to heart, blood vessel, lung, and blood diseases; and (2) directed the Institute to lead and coordinate the nation's attack on these diseases through the implementation of that Program.

As the content of the previous chapters demonstrates, the Program after five years is national in scope and impact, complex and multifaceted, and involves many disciplines and organizations. It encompasses a wide spectrum of research activities directed toward increasing our knowledge of disease etiology and pathogenesis and improving our capability to diagnose, treat, prevent, and control the cardiovascular, pulmonary, and blood diseases on which the National Program is focused.

This chapter examines the influence of legislation on the Institute's mandates and describes the planning, implementation, evaluation, and coordination processes and activities through which the NHLBI carries out its legislated programs.

NHLBI LEGISLATION IN RETROSPECT

In enacting the National Heart Act (P.L. 655), which established the National Heart Institute in 1948, Congress recognized the need "to improve the health of the people of the United States through the conduct of research, investigations, experiments, and demonstrations relating to the cause, prevention, and methods of diagnosis and treatment of diseases of the heart and circulation." In its early years of operation, the National Heart Institute initiated and supported basic research programs to discover the mechanisms underlying cardiovascular diseases and to develop methods of controlling and treating them. During the following two decades, the Institute expanded and improved on those efforts.

By 1972, biomedical research capabilities and the national interest in health research had matured to the point of stimulating a major reassessment of the Institute's role. The most significant result of this reassessment was the formulation and enactment, by Congress, of the National Heart, Blood Vessel, Lung, and Blood Act of 1972 (P.L. 92-423). The new law strengthened the purpose of the National Heart Act, declaring: "It is the purpose of this Act to enlarge the authority of the National Heart and Lung Institute in order to advance the national attack upon heart, blood vessel, lung, and blood diseases."* The resulting National Program was to "provide a coherent program for action and for evaluation."[1] Program directives covered a comprehensive range of heart, lung, and blood research, all coordinated by a five-year national plan to be annually updated in a Director's Report to the President and Congress.

Recognizing that "the most important single factor in the control of any disease is prevention,"[2]

* The National Heart Institute had been redesignated the National Heart and Lung Institute in 1969 by the Secretary of Health, Education, and Welfare to reflect its growing functions.

[1] Senate Report No. 92-733, page 29.

[2] House Report No. 92-1108, page 5.

Congress integrated into the National Program research in prevention, an Assistant Director for Health Information Programs, and the establishment of Research and Demonstration Centers. To help ensure an effective program, the 1972 legislation strengthened the Institute's National Advisory Council to perform its many roles, established the Interagency Technical Committee (IATC) to foster Federal program coordination, and directed minimum 15 percent budget allocations for the lung and blood programs.

In the legislative reauthorization in 1975, Congress reaffirmed its support of the Institute's programs. The resulting Health Research and Health Services Amendments of 1976 (P.L. 94–278) continued National Program activities in heart, lung, and blood disease research with the addition of expanded responsibilities for research in blood, blood products, and the management of blood resources. To reflect and emphasize this expansion, Congress renamed the Institute the National Heart, Lung, and Blood Institute and renamed its major advisory body the National Heart, Lung, and Blood Advisory Council. Congress also reaffirmed its concern about prevention, redesignating the Assistant Director for Health Information Programs as the Assistant Director for Prevention, Education, and Control.

LEGISLATIVE PROCESS AND IMPACT

Progress in biomedical science requires a combined nontargeted and targeted research approach. Non-targeted research, which increases the base of scientific knowledge, yields practical results in a serendipitous fashion—e.g., when a fundamental research effort helps elucidate a disease mechanism or when a discovery about one disease mechanism has unexpected applications to another. When an adequate fundamental science base exists, targeted research is initiated to expand the knowledge and provide methods for its transfer into useful clinical techniques.

The ongoing, interactive, and repetitive nature of the legislative process ensures that, through the regular reevaluations which are an integral part of the authorization and appropriation cycles, Congress can coordinate mandates and resources with progress in biomedical science and formulate specific mandates which focus on major themes, initiate operational changes, or identify specific research areas.

The rapidity with which a specific congressional mandate is translated into an operational program varies according to the scope and duration of the program and the magnitude of the resources required. While the fulfillment of mandates and the impact of legislation are not always easily discernible, the Acts of 1972 and 1976 have had a significant impact on the National Heart, Lung, and Blood Institute and its programs. Several brief examples may help illustrate this point.

- The 1972 Act calls for, and has resulted in, broadening of the kind of research sponsored by the Institute (e.g., clinical trials, etiology and epidemiology*) and the extension of certain programs. For example, the Act specifically calls for increased emphasis on diseases of children. Based on this mandate, the Institute has initiated a number of research programs. One of these, which has markedly improved the management of neonatal respiratory distress syndrome, holds promise for even more effective prevention and control of this disorder. Substantive programmatic changes related to blood give the Institute a broadened mandate for coordinating and integrating NIH programs related to blood diseases and blood resources. In response, an NIH Coordinating Committee for Blood-Related Activities was established in 1976, with the Director of the National Heart, Lung, and Blood Institute serving as chairman. All other Institutes having any significant interest in blood-related activities are represented on the Committee.
- The legislation also authorized separate funding levels for prevention, education, and control programs. However, separate appropriations have never been made, and funds for such programs have had to come from the overall research appropriation. Thus, the legislative provisions for prevention, education,

* See Chapters 1 and 2 for descriptions of clinical trials and etiological and epidemiological investigations supported by the Institute.

and control programs have had a positive effect—increased emphasis on such programs —and a negative effect—a reduction in resources available for research. Nevertheless, the Institute has developed significant programs in this area. One of these, the National High Blood Pressure Education Program, was initiated during the summer of 1972. It is achieving its goal of reducing death and illness associated with hypertension through education programs directed at both the general public and health professionals.*

- The legislation also provides for the "establishment of programs that will focus and apply scientific and technological efforts involving the biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases, with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improved instrumentation for detection, diagnosis, and treatment of those diseases."[1] Currently, several NHLBI programs are exploring the application of sophisticated noninvasive techniques to the detection and diagnosis of cardiovascular and pulmonary disorders.** Diagnostic techniques that involve no surgery are associated with lower patient risk than are invasive methods, and are usually more easily and less expensively administered.
- The legislation authorizes the NHLBI Advisory Council to review NHLBI projects and programs, including grant applications, and to certify its approval of such applications. The 1976 Act includes a specific provision authorizing the Council to recommend to the Secretary of Health, Education, and Welfare areas of research which should be supported by the awarding of contracts and the percentage of the Institute's budget which should be expended for such contracts. In response, the Institute, as an integral part of its planning process, prepares a plan for implementing Institute-initiated programs for the fiscal year, including those areas to be supported by contracts. As required by the 1976 Act, this plan is presented to the Council, at a special annual meeting, for its review and recommendations prior to implementation.

Nineteen seventy-seven marks the fifth year of the National Program initiated by the 1972 legislation. This year, Congress is again utilizing the dynamics of the legislative process to critically examine several health program areas, including research. During this "year of biomedical overview," a one-year reauthorization is maintaining health programs while Congress, the Administration, and the public review together the biomedical goals and progress of the National Program.

PLANNING, EVALUATION, AND COORDINATION

Planning

The initial five-year plan was developed through the combined efforts of the NHLBI; the National Heart and Lung Advisory Council; four national panels of consultants on heart and blood vessel diseases, lung diseases, blood diseases, and blood resources; the Interagency Technical Committee, comprising representatives of Federal agencies; and 28 task groups. Additional assistance was provided by a number of nonprofit voluntary agencies, public interest groups, and the scientific community. This collaboration promoted productive interaction and joint planning among those at the forefront of the fields that make up the scientific constituency of the Institute, those responsible for carrying out the National Program, and those ultimate "consumers" of the results of the Institute's programs. The resulting Plan forms the basis for the Institute's many programs and for its annual cycle of program planning, evaluation, and coordination (Figure 10).

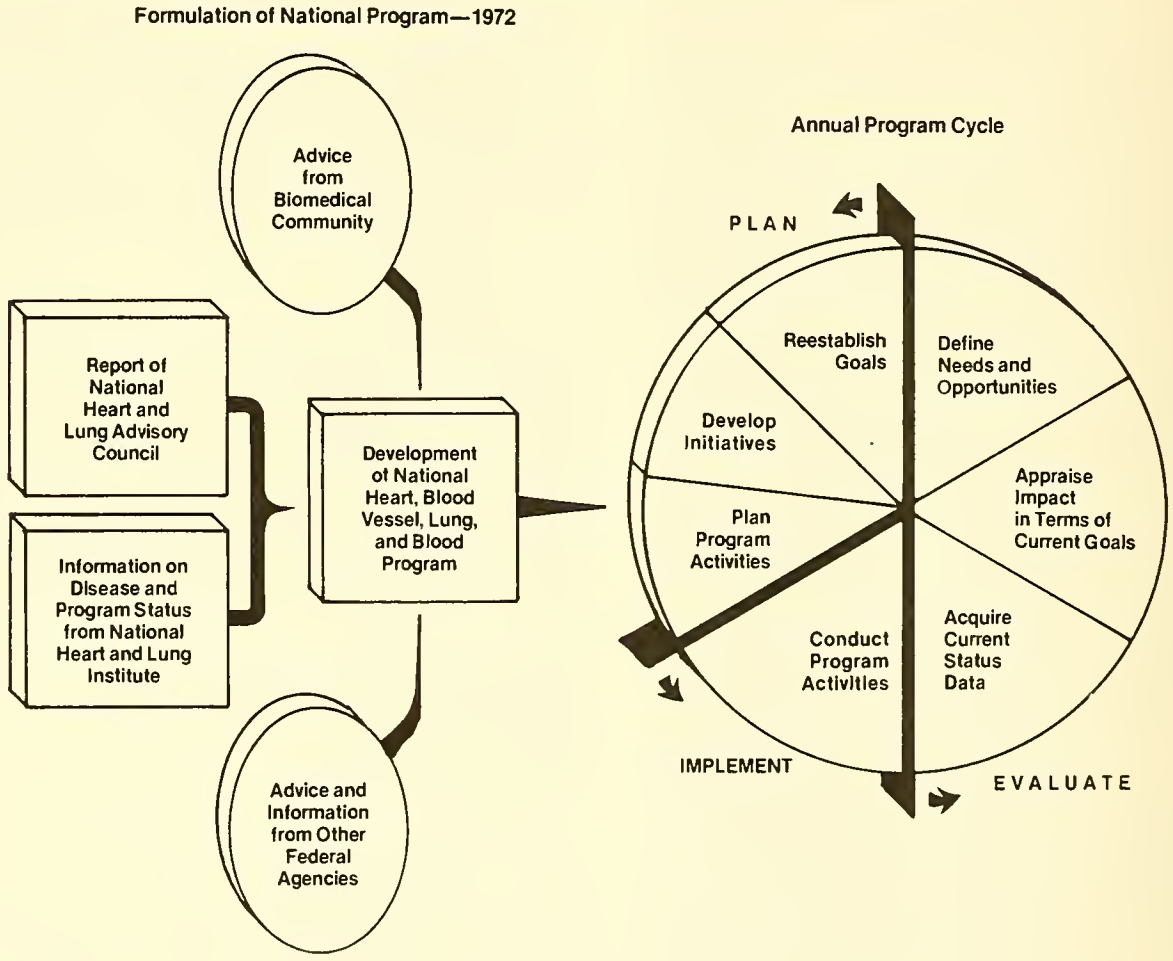
The nature of planning, as it is carried out by the Institute, is a continuous process encompassing

* See sections on hypertension in Chapter 2 and in Chapter 3.

[1] Public Health Service Act, Section 413(a)(4).

** See Chapter 2 for descriptions of specific programs involving noninvasive methods of detection and diagnosis and other programs involving devices and instrumentation.

Figure 10: ORIGIN OF THE NATIONAL PROGRAM AND THE ANNUAL PROGRAM CYCLE



activities ranging from the development of policies and strategies at the national level, through the setting of priorities among competing programs, to the establishment of budgets for single programs or projects. Planning approaches vary. Some are highly specific, controlled techniques; others are relatively unstructured approaches with the flexibility necessary to promote research leading to important biomedical innovations.

The NHLBI planning process is a yearly cycle characterized by a continuous flow of information from the public, the biomedical research community, the medical community, other Federal agencies, and non-Federal organizations. The Institute is responsible for coordinating this input and developing it into meritorious programs to be implemented within existing resource constraints.

As part of this planning process, a series of reports and formal plans are published each year. These documents, which serve as milestones in the annual planning process, are prepared by NHLBI staff members to structure and coordinate input from the NHLBI Advisory Council and from NHLBI committees and consultants. The documents serve as resource materials, implementation plans for program activities, and state-of-the-art assessments.

They define program component interrelationships, inform Congress and the Administration of needs for accomplishing the five-year plan, and inform the scientific community of accomplishments. However, the planning process—not the documents—is key to the orderly development and implementation of the Institute's programs. Coordinated and timely involvement of those responsible for guiding the NHLBI ensures that the resultant plans and reports are dynamic and meaningful.

The NHLBI planning process consists of four distinct but overlapping steps leading to the implementation of new programs or to the expansion, modification or discontinuation of existing programs (Figure 11).

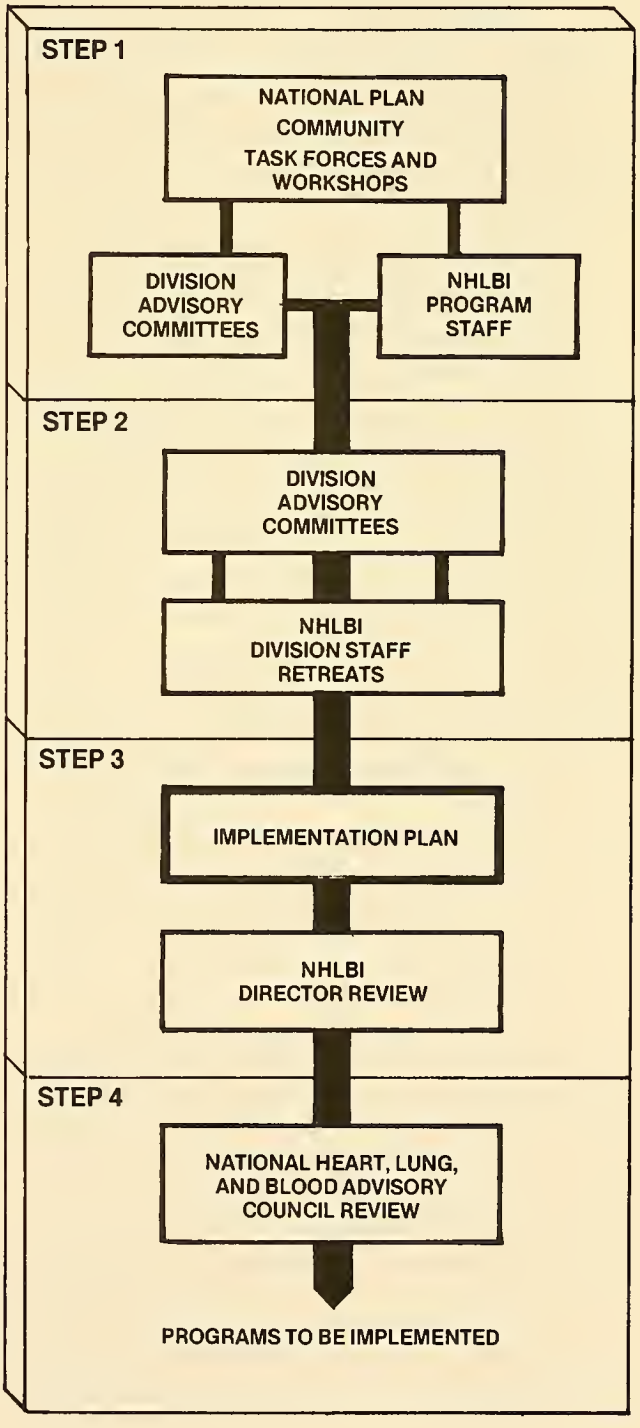
- **Step 1.** The first step in the process—review, assessment, and consensus—is centered on a series of intensive interactions among the NHLBI program staff, the Institute's scientific advisory committees, and members of the general scientific community. (Chartered NHLBI advisory committees are listed in Table 12.) Through an interactive process using workshops, seminars, task forces, and technical working groups, the goals, objectives, and progress of the National Program Plan are reviewed against the state of the science reflected in the published scientific literature and the collective knowledge of the participating scientific experts. During this process, existing research strategies are examined and new ones developed. The

Table 12

NHLBI COMMITTEES ASSISTING IN PROGRAM ASSESSMENT

CARDIOVASCULAR
Arteriosclerosis and Hypertension Advisory Committee
Cardiology Advisory Committee
Lipid Metabolism Advisory Committee
Clinical Applications and Prevention Advisory Committee
PULMONARY
Pulmonary Diseases Advisory Committee
BLOOD
Blood Diseases and Resources Advisory Committee
Sickle Cell Disease Advisory Committee

Figure 11: THE NHLBI PLANNING PROCESS



major tangible product of this first step in the planning process consists of preliminary lists of recommended program initiatives for the ensuing program years.

- **Step 2.** The second step in the process—priority setting—is accomplished jointly by the program staff of each of the Institute's categorical divisions and the appropriate advisory committee. During this step, new initiatives are ranked according to the goals and objectives of the National Plan and are rated and ranked by groups of experts in their respective program areas. Based on the advice and recommendations of these experts, NHLBI staff members further develop the more promising initiatives in light of the progress, results, and potential impact of ongoing programs; fiscal and schedule constraints; and program objectives. The surviving initiatives are further reviewed and approved by the respective advisory committees. The tangible product of this step is a list of categorized and prioritized initiatives.
- **Step 3.** The third step in the planning process —implementation plan development and review—is conducted within the Institute. Each categorical division prepares an implementation plan outlining each new initiative in terms of its scientific and programmatic rationale and justification, funding mechanism, and management and fiscal plan. The Institute Director's office reviews and analyzes each implementation plan and adjusts it to reflect total available resources, congressional mandates and intra-Institute, inter-Institute, and interagency programmatic responsibilities. The adjustments are reviewed and negotiated with each categorical division. The result of this step is the NHLBI Implementation Plan and Program Budget.
- **Step 4.** The fourth step in the process—National Advisory Council review—provides for direct Council participation in the planning process. Each new program initiative or major program expansion is presented to, and reviewed by, the entire Advisory Council during open session. Council recommendation is solicited and obtained on each initiative, and Council advice on special areas for emphasis is received. After Advisory Council review, the initiatives and other recommendations resulting from this intense, thorough, and disciplined planning process are ready for implementation.

Program Implementation

The NHLBI is structured and organized to most effectively achieve those objectives and implement those programs contained in its authorizating legislation. However, it is a task of considerable magnitude to ensure the continuing responsiveness of the Institute to evolving national needs, to corresponding changes in congressional mandates, and to the state of the science. Furthermore, since mandates normally are broadly stated and have widespread implications, programs developed to fulfill mandates vary in scope and direction: Some may impact on a large segment of the population, while others impact on a specific fraction needing a solution to a particular problem.

Thus, program implementation is a complex process requiring the availability and optimum utilization of scientific knowledge, human and financial resources, and facilities. The rapidity with which a specific mandate or approved initiative is translated into an operational project depends to a large degree on the availability of the resources required. Implementation of the Institute's program is only possible through considerable pre-planning, coordination of required resources, sound program management, and the interest and collaboration of dedicated experts in the scientific community.

Evaluation

The Institute's responsibility does not end with program planning and implementation. There is the continuing need to evaluate the National Program against specific goals and objectives outlined in the initial Five-Year Plan, and assess the state of the science in areas covered by the NHLBI mission, identify needs, and capitalize on opportunities. These requirements are fulfilled by a diverse set of activities combined into a disciplined strategy. The

Institute's evaluation activities include:

- Collection and analysis of data on small projects and large programs.
- Acquisition of expert scientific judgment of ongoing programs.
- Assessment of the resultant or potential effectiveness of concluded programs.
- Complete analysis of stated National Program goals, planned actions, and scheduled activities.

Coordination

An important part of the responsibilities of the NHLBI with respect to the National Heart, Blood Vessel, Lung, and Blood Program is coordination of those aspects of Federal health programs which relate to cardiovascular, pulmonary, and blood diseases and blood resources.

The Institute's mandate includes program coordination at both the NIH and the overall Federal levels. Within NIH, the NHLBI coordinates the National Program with the other National Institutes of Health to the extent that they share responsibility for research on diseases included in the Program.

At the Federal level, an Interagency Technical Committee (IATC) is mandated to coordinate "those aspects of all Federal health programs and activities relating to heart, blood vessel, lung, and blood diseases, and to blood resources, to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities."

Established subsequent to passage of the 1972 legislation, the IATC is chaired by the Director of the NHLBI. It includes representatives of all Federal departments and agencies with health functions and responsibilities. These departments and agencies are listed below:

- National Heart, Lung, and Blood Institute
- All other NIH Bureaus, Institutes, and Divisions
- Center for Disease Control
- Department of Agriculture
- Department of Defense
- Department of Transportation
- Department of Energy
- Environmental Protection Agency
- Food and Drug Administration
- Health Resources Administration
- Health Services Administration
- National Aeronautics and Space Administration
- National Institute of Mental Health
- National Science Foundation
- Rehabilitation Services Administration
- Social Security Administration
- Veterans Administration

Through the use of interagency technical working groups focused on specific research areas and through the use of interagency reimbursable agreements, the Institute promotes the cross-utilization of specialized expertise and facilities necessary to conduct multidisciplinary research and launch multifaceted demonstration and education programs. This mechanism serves to promote cross-fertilization of ideas, to minimize duplication of effort among Federal agencies, and above all, to maximize the use of increasingly sparse resources—both manpower and dollars.

Following are examples of specific programs involving the collaboration of the NHLBI and one or more other Federal agencies.

BLOOD SAFETY

. . . Sterile Connecting Device

The need for red blood cells accounts for 70 percent of all blood transfusions. Red blood cells can be maintained for many months without quality loss when stored in a frozen state. Because processing methods do not guarantee sterility, however, *Food and Drug Administration (FDA)* regulations require that frozen blood cells be used within 24 hours once thawed. To solve this problem, a new technique—the sterile connecting device—has been developed to allow blood bank personnel to thaw red blood cells and selectively remove fractions while maintaining the sterility of the remainder. Recently

completed tests showed that even after 10 transfer operations through the sterile connecting device, sterility was maintained, and the half-life of the cells remained unchanged. The FDA is now considering licensure of the use of this device, which would substantially increase the safe storage time of all red blood cell products and reduce wastage due to outdating of products before they can be used.

PRESERVATION OF RED BLOOD CELLS

. . . New Additive Extends Shelf Life

It has been demonstrated that the addition of adenine to red blood cell preservative solutions permits extension of the storage period for red cells from 21 to 35 days. Results of recent studies were presented at a workshop jointly sponsored by the NHLBI and the *FDA's Bureau of Biologics'* Panel on Review of Blood and Blood Derivatives. The workshop concluded with a recommendation to the panel for the licensure of adenine as an additive to extend the outdating period of stored liquid red blood cells. The impact of this action will be reflected in a better product at the old outdating period of 21 days and in an opportunity for better inventory management as a result of extending the outdating period to 35 days.

NUTRITION AND HEALTH

. . . New Information on Food Composition

In conjunction with NHLBI, two agencies of the *Department of Agriculture* are working to rectify the deficiency of adequate data on food composition. The Consumer and Food Economics Institute is searching current scientific literature for information on lipids in foods, new processing techniques, food product development, and fatty acid composition. These data are being used to form a computerized file which will aid in calculating fatty acids in baked goods, main dish casseroles, ethnic dishes, desserts, and other foods. The Nutrient Composition Laboratory analyzes the nutrient content of food components that are identified by NHLBI as nutritionally important. The resulting data, disseminated through the cooperative efforts of NHLBI and the Department of Agriculture, provide vitally needed information for the fight against heart and vascular diseases.

MEAL PLANNING GUIDES

. . . Special Diets for Treatment of Disease

The NHLBI is also collaborating with nutritionists of the American Diabetes Association, the National Institute of Arthritis, Metabolism, and Digestive Diseases, and the American Dietetic Association to prepare and publish *Exchange Lists for Meal Planning*. This publication contains updated data on food composition and reflects current approaches to nutrition education. It encourages the use of fat-controlled diets as treatment for diabetes, obesity, and other diseases for which special diets are necessary.

DRUG TREATMENT FOR HYPERTENSION

. . . Understanding the Uses of Propranolol

The *Veterans Administration* and NHLBI have jointly studied the efficacy and safety of the drug propranolol as a treatment for hypertension. Over 400 patients participated in this 18-month study; its results yielded a clearer understanding of the benefits and limitations of propranolol as a treatment for hypertension.

PREHOSPITAL EMERGENCY CARE

. . . Its Effect on Cardiac Victims

In collaboration with the *Department of Transportation,* NHLBI is undertaking an investigation to identify and analyze studies that describe prehospital emergency care for cardiovascular victims in the United States. Specifically, the study will attempt to determine the data collection requirements needed to estimate the effectiveness of emergency medical systems on cardiovascular care. Study results are expected to indicate where research on these systems may improve the prognosis of heart disease patients, as well as provide government agencies with useful data that will help them plan programs responsive to current and future needs.

TRAINING PHYSICIANS IN PATIENT EDUCATION

. . . Curriculum Materials for Primary Care Providers

Curriculum materials have been devised by the Interagency Working Group on Training of Physicians for Patient Education. Films and instructional

manuals will introduce trainers and trainees of family practice programs to patient education needs and strategies. A Working Group member, the Bureau of Health Education of the *Center for Disease Control,* is promoting the establishment of a clearinghouse to collect, review, and disseminate patient education materials to primary care providers. Under the sponsorship of the Working Group, a task force of experts in patient education and curriculum development is currently at work on guidelines specifying the knowledge and attitudes toward patient education that physicians should have by the time they complete residency training.

COMPREHENSIVE STUDY OF CYSTIC FIBROSIS

. . . Results to Be Published in 1978

A state-of-the-art assessment of cystic fibrosis research, professional education, and patient care activities is under way by the Cystic Fibrosis Foundation. The study, jointly funded by NHLBI and the *National Institute of Arthritis, Metabolism, and Digestive Diseases,* will also project future trends in these areas. Considerable interest and a desire to participate in this project have been expressed by many of the other NIH Institutes. A Cystic Fibrosis Coordinating Committee has been appointed with representatives from each Institute concerned with research on the disease. The Director, NIH, has assigned a special assistant as chairperson of the Committee. Health-related agencies outside of NIH are also expected to take part in the assessment of cystic fibrosis.

COMPUTERIZED CHEMICAL INFORMATION

. . . International Participation

Domestic and foreign government agencies, private corporations, and universities can obtain computerized chemical data instantaneously from the Chemical Information System developed jointly by the National Institutes of Health and the *Environmental Protection Agency.* Accessible via satellite, the system allows intercontinental, 24-hour availability of its data base by local telephone on a fee-for-service basis.

The Chemical Information System, which maintains a centralized data bank on chemical information, thereby eliminating the fragmentation of many separate data systems, supplies physiochemical data and bibliographic entries and abstracts of scientific papers. This information is used for a variety of scientific purposes: EPA obtains data on toxic substances, NHLBI gathers data on biologically important compounds, and the Food and Drug Administration uses the data base to identify unknown chemical compounds.

BLOOD COAGULANTS FOR HEMOPHILIACS

. . . Demand Will Not Exceed Supply

In collaboration with the *Health Services Administration,* NHLBI funded a study to estimate the quantity of blood plasma products needed by hemophiliacs and the extent to which their needs might surpass supplies by 1980. The study concluded that the demand will increase at a moderate rate over the next five years, and that the supply each year will be adequate to meet the needs of the nation's hemophiliacs.

8. TRAINING AND MANPOWER DEVELOPMENT PROGRAMS

THE NEED FOR TRAINED MANPOWER

The preceding chapters have indicated the tremendous magnitude of the challenges facing the NHLBI and the broad scope of the research programs through which the Institute strives to meet those challenges. The success of these programs is dependent upon the availability of well-trained research scientists and clinicians in a wide array of fundamental and clinical research areas.

Accordingly, the NHLBI is committed to the policy that research training and manpower development are essential to the implementation of a responsive, high quality National Program directed toward the prevention of cardiovascular, pulmonary, and blood diseases and the control of their complications, and to the availability, to all Americans, of an adequate and safe blood supply.

In all areas of the Institute's programs, there is a documented need to train scientists in the many disciplines which need to work together to solve the complex scientific and clinical problems within the NHLBI mandate. And as this mandate continues to be increased and the Institute's programs evolve and grow in response, the need for trained scientists will grow well beyond that required for replacing more senior colleagues who retire or move out of research and teaching into administration or other endeavors.

During the last few years, several professional societies have assessed the needs for professional manpower in heart, lung, and blood research. The American College of Cardiology, the American Heart Association, the American Association for Thoracic Surgery, the American Thoracic Society, the American College of Chest Physicians, the American Lung Association, the American Society of Hematology, and the American Medical Association have all performed assessments of training needs in their areas of concern. Specific requirements have been identified for behavioral scientists; chemists and investigators with specialized training in endocrinology; experts on blood coagulation; blood banking personnel; individuals with expertise in fundamental nutrition, lipid metabolism, growth and development, and pediatrics; and epidemiologists and biostatisticians. Currently, there is an exceptional need for nutritionists and epidemiologists to fill existing vacancies in important new programs which have evolved in response to the 1972 National Heart, Blood Vessel, Lung, and Blood Act. These programs include the Institute's Specialized Centers of Research; National Research and Demonstration Centers; the large collaborative clinical trials; and programs related to prevention, education, and control.

PROGRAM RESPONSE

Based on assessments such as these as well as those of the National Research Council and the National Academy of Science, and on the recommendations of the Institute's Advisory Council, the NHLBI has, within the constraints of available resources, placed high priority on increasing the number of investigators trained in fundamental and clinical research related to cardiovascular, pulmonary, and blood diseases.

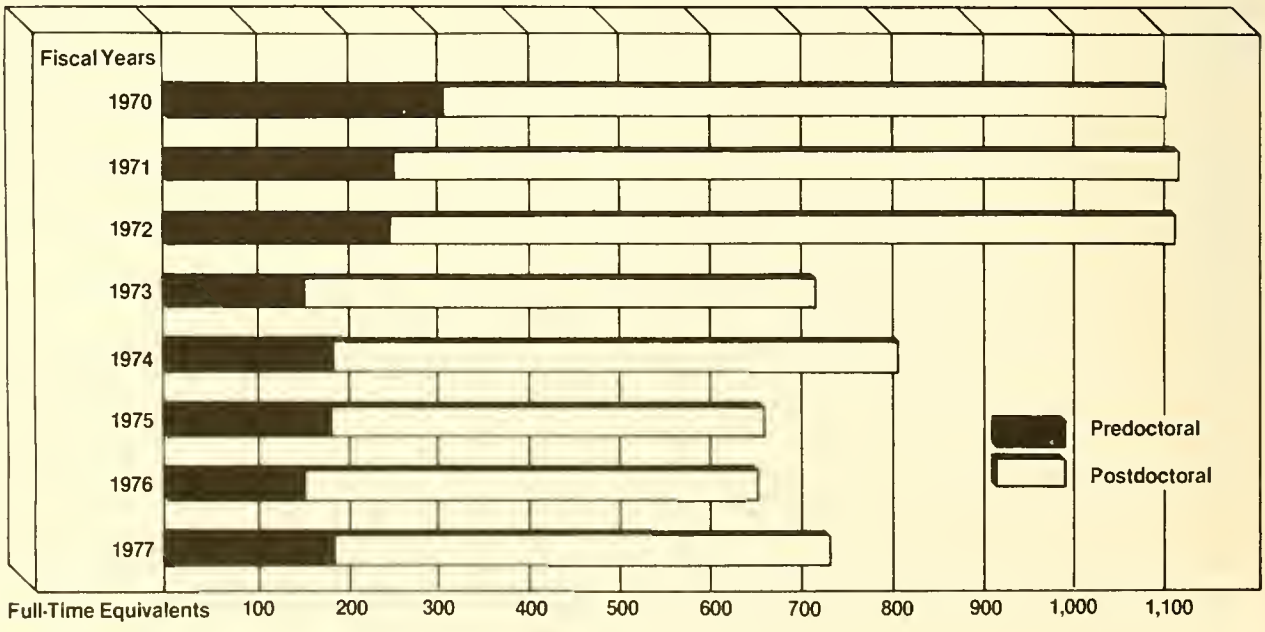
Table 13

NUMBER OF TRAINEES BY ACTIVITY (FULL-TIME EQUIVALENTS), FISCAL YEARS 1970-1977

Training Program	1970	1971	1972	1973	1974	1975	1976	1977
Postdoctoral and Special Fellowships	176	168	144	72	36	10	1	—
Individual Research Fellowships	—	—	—	—	167	56	43	2
Individual NRSA[1]	—	—	—	—	—	138	193	188
Subtotal Individual Fellowships	176	168	144	72	203	204	237	190
Graduate Training Grants	1,225	1,265	1,225	1,100	1,065	690	449	233
Pulmonary Faculty Training Centers	—	—	—	—	—	24	24	24
Institutional NRSA[1]	—	—	—	—	—	279	491	712
Subtotal Institutional Fellowships	1,225	1,265	1,225	1,100	1,065	993	964	969
Total: NHLBI Training Programs	1,401	1,433	1,369	1,172	1,268	1,197	1,201	1,159

[1]NRSA = National Research Service Award

Figure 12: TRAINING PROGRAMS IN HEART AND VASCULAR DISEASES, FISCAL YEARS 1970-1977



Yet as a result of (1) a number of changes in the nation's policy regarding biomedical research training and (2) the limited resources available for the support of training programs, the number of individuals trained in areas within the Institute's mandate has not begun to keep up with the demand (Table 13). The decrease in trainees supported by Institute programs since the peak year of 1971—19 percent—is of great concern because it has occurred during a time when the need for trained investigators has increased significantly.

Of particular concern to the NHLBI is the alarming decrease in personnel training in the cardiovascular field (Figure 12). This decrease—approximately 34 percent since 1971—is partially masked in Table 13 by increased numbers of trainees in the lung and blood areas, the mandates for which were added to the Institute in 1972. Continuation of this downward trend will mean fewer trained scientists and clinicians performing cardiovascular research at a time when the potential for making significant progress toward the prevention of heart and blood vessel diseases and the effective control of their complications is so great.

National Research Service Awards

The National Research Service Award (NRSA) Act of 1974 repealed previous research training authorities of the NHLBI. Therefore, in accordance with this legislation, previous fellowship and traineeship programs are in the process of being phased out. Under the NRSA legislation, the NHLBI may make both individual and institutional training awards in areas of specified shortage and relevance to its programs. The NHLBI places great emphasis on post-doctoral training because this type of training can supply the multidisciplinary personnel required to carry out its programs.

The National Research Service Award for individual post-doctoral fellows, first made in 1975 and now used throughout the Institute, supports post-doctoral fellows in specified areas of biomedical and behavioral research in which a documented need for trained manpower exists. The success of this fellowship program is based on the historical fact that the more inquiring young investigators are attracted to emerging fields and that their involvement in those fields stimulates research programs.

The National Research Service Awards for institutional research training are given to eligible institutions to develop or enhance research training opportunities for both pre-doctoral and post-doctoral candidates interested in careers in specified areas of biomedical and behavioral research. The institutional NRSA encourages departments to build comprehensive and scholarly programs so that they can provide high quality and established faculty to interact with trainees. The five-year period of the institutional NRSA grant permits the long-range stability essential for program coherence and cohesiveness.

Both of these types of NRSA fellowships are vital to the Institute's research programs. Accordingly, the Institute places high priority on increasing the number of both individual and institutional National Research Service Awards.

Research Programs Emphasizing Scientific Manpower Development

Innovative manpower development programs are being pursued in relation to the new and unique NHLBI missions defined by recent legislation. These programs are planned and tailored to specific requirements and opportunities. As a result, some of the NHLBI manpower development programs are considered as research activities rather than as training programs and are, accordingly, supported by research funds. Such programs include the following:

- **The Minority Hypertension Research Development Summer Program** is designed to foster the recruitment and development of minority health manpower to work in areas of research related to hypertension. The program, which enables minority school faculty and graduate students to receive summer training in institutions with demonstrated excellence in hypertension-related research and training, exposes these individuals to career opportunities in hypertension research at a very early phase of their career development. It is anticipated that, as a result of this program, there will be an increase in the

This scientist is using an ultra-microtome to make thin sections of a strip of arterial wall muscle. The research objective is to conduct an ultrastructural study of the nerve supply of vascular smooth muscle in normal and hypertensive mammals. This project is part of the Minority Hypertension Research Development Program.

number and kinds of persons drawn from minority communities who are especially trained in health research and will commit themselves to careers in areas of investigation related to hypertension. Furthermore, it is hoped that these minority trainees will return to their own institutions and stimulate their peers to participate in this or similar biomedical research programs.

- **The Minority Biomedical Research Support Program** is a cooperative effort through which the Institute encourages research participation in an ethnic minority program administered by the NIH Division of Research Resources. The program is designed to increase the numbers and broaden the biomedical research opportunities of ethnic minority faculty, graduates, undergraduates, and investigators. Projects that relate to the overall mission of the NHLBI are funded through the Institute. Scientific guidance is provided to grantees by Institute staff in close coordination with the staff of the Division of Research Resources.
- **Minority Access to Research Careers (MARC) Program,** administered by the National Institute of General Medical Sciences, is designed to help minority institutions train greater numbers of scientists and teachers in the biomedical disciplines. The MARC Faculty Fellowship Program provides opportunities for advanced research training for selected faculty members of four-year colleges, universities, and health-professional schools in which student enrollments are drawn substantially from ethnic minority groups. The MARC Visiting Scientist Award provides financial support which allows outstanding scientist-teachers to serve in the capacity of visiting scientists at these same kinds of institutions.
- **The National Pulmonary Faculty Training Program** is designed to strengthen pulmonary faculties in schools of medicine and schools of osteopathy and enrich their training environments through the training of junior faculty members at specialized cooperating medical centers. The first centers were designated in 1975 and the first group of junior faculty members were selected for training in 1976.
- **The Pulmonary Academic Award Program,** initiated in 1971, supports students at 45 medical schools. The aims of this program are to foster a stimulating approach to the diagnosis and treatment of respiratory diseases, to attract medical students to pursue respiratory medicine, to facilitate careers of teacher-investigators, and to encourage schools to recognize respiratory diseases as a subspecialty. A symposium on this program, conducted at the fall 1977 meeting of the Association of American Medical Colleges, served to increase the program visibility.
- **The Young Investigator Research Grant Program** was introduced as a specialized lung disease program in 1974. The initial success of this program in attracting excellent beginning investigators resulted in its expansion to include all NHLBI programs in 1976. The Young Investigator Research Grant Program provides modest support for first research grants designed by beginning investigators pursuing fundamental and clinical projects.
- **The Research Career Development Award Program** was initiated by NIH in 1961 to increase the number of stable positions for outstanding scientists near mid-career. The current program has evolved so that it now invites applications from individuals with outstanding potential who are considerably more junior than the original awardees, but who require additional training and experience in a productive scientific environment as preparation for a career in independent research.
- **Special Emphasis Research Career Award (SERCA) in Diabetes Mellitus: Cardiovascular, Metabolic, and Endocrinologic Aspects,** a new program to be implemented in 1978 by the NHLBI and the National Institute of Arthritis, Metabolism, and Digestive Diseases, differs from existing NIH awards in both con-

cept and scope. It provides the opportunity for an individual with developing research interests to acquire experience and skills in the broad fundamental and clinical scientific disciplines essential for a multidisciplinary approach to the study of the metabolic, endocrinologic, and cardiovascular aspects of diabetes mellitus. The SERCA emphasizes in-depth experience in several fundamental and clinical scientific disciplines which are not dependent upon a single laboratory or institution.

PROSPECTS FOR MEETING THE INCREASING NEED

The NHLBI continues to assess the manpower needs of the National Program and to determine areas in which a critical manpower pool is lacking. Most recent analyses indicate that the scientific manpower needed to support the full range of activities defined by the National Program is deficient in a number of areas. And the general prospect for the next few years is a continued rising demand for new entrants into heart, lung, and blood disease research. While the existing manpower pool is expected to provide adequately for some specific program area needs, critical research areas (e.g., epidemiology, behavior, nutrition, blood banking, academic cardiology, and pulmonary diseases) are thwarted by shortages of specialized personnel.

As shown by Figure 12, in 1971, the Institute's program supported over 1,100 trainees whose research is now contributing to the steady decline in cardiovascular mortality. However, because of frequent modifications in training programs and the lack of adequate fiscal growth, there has been a steady decline in the number of trainees in this area until lows of fewer than 700 were reached in 1975 and 1976. Even though concerted Institute efforts in 1976 have led to a modest increase in the number of trainees, we are still far below the number trained in 1971 and are not even beginning to meet the levels required by increased cardiovascular research activity.

Special emphasis programs in both the manpower and research areas have resulted in increased manpower for the pulmonary research area. However, pulmonary researchers are still in short supply, limiting the growth of research activities in an area marked by increasing morbidity and mortality. Similarly, there is a critical need for trained blood bank and blood research personnel to ensure fulfillment of the goals of the nation's blood policy. Although there has been slow but steady progress in meeting the nation's needs for researchers in the areas of blood diseases and resources, the progress is far from adequate to meet projected needs.

The challenge seems clear. For the NHLBI to continue the progress shown in previous chapters toward the prevention of cardiovascular, pulmonary, and blood diseases, the effective control of their complications, and the provision of an adequate and safe blood supply, and to meet the ambitious goals established for the next five years, a cadre of scientists and clinicians trained for research in these areas must be maintained. This will require training and manpower development programs which are backed by adequate resources, which have sufficient flexibility to permit expansions required by research and program needs, and which are stable enough to permit long-range planning by the Institute and by collaborating academic centers.

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